

✓ Valine and Phenylglycine based Chiral Nonracemic Ligands in Asymmetric Synthesis

A Thesis Submitted
in Partial Fulfilment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

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to the
DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR
INDIA

STATEMENT

I hereby declare that the matter embodied in this thesis entitled "VALINE AND PHENYLGLYCINE BASED CHIRAL NONRACEMIC LIGANDS IN ASYMMETRIC SYNTHESIS" is the result of investigations carried out by me in the Department of Chemistry at Indian Institute of Technology (I.I.T) Kanpur, India, under the supervision of Dr. Vinod K. Singh.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the finding of other investigators.

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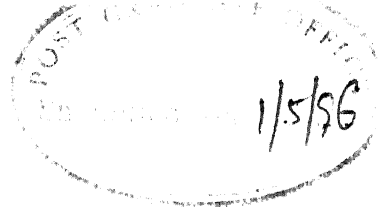
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CERTIFICATE I



ii

It is certified that the work contained in this thesis entitled "VALINE AND PHENYLGLYCINE BASED CHIRAL NONRACEMIC LIGANDS IN ASYMMETRIC SYNTHESIS" has been carried out by Ms. Arpita DattaGupta, under my supervision and the same has not been submitted elsewhere for a degree.

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CERTIFICATE II

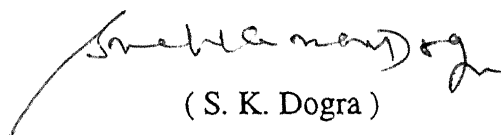
This is to certify that Ms. Arpita DattaGupta has satisfactorily completed all the courses required for the Ph.D. programme at our department. These courses include:

CHM 605	Principles of Organic Chemistry
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CHM 664	Modern Physical Methods in Chemistry
CHM 681	Basic Biological Chemistry
CHM 800	General Seminar
CHM 801	Special Seminar
CHM 900	Ph.D. Thesis

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I.I.T. Kanpur

Arpita DattaGupta

SYNOPSIS

The thesis entitled "VALINE AND PHENYLGLYCINE BASED CHIRAL NONRACEMIC LIGANDS IN ASYMMETRIC SYNTHESIS" is divided into four chapters. The title of each chapter and the related summary is given below.

Chapter 1: Enantioselective Cyclopropanation Reactions.

In this chapter, we describe the synthesis of metal complexes of new chiral bis(oxazolinyl)pyridine(pybox) type ligands for the enantioselective cyclopropanation reaction of olefins. The reactions were tried under different conditions. Sterically hindered diazoester increases both the diastereoselectivity and enantioselectivity. CHCl_3 turned out to be the best solvent for the reaction of styrene with *tert*-butyl diazoacetate. Although the reaction was not very enantioselective but the diastereoselectivity was found to be high. The enantioselectivity was determined based on the shift reagent study. We have also thrown light on the mechanistic aspects of the reaction. With the help of uv-visible and epr spectroscopy, we have proved that the reaction is catalyzed by Cu(I) and this is formed, *in situ*, at room temperature by the reduction of Cu(II) complex with the diazoester used in the reaction. Thus, the activation of Cu(II) catalysts by external means is not needed for this kind of reaction. The facial selectivity of the reaction is explained based on a copper carbenoid transition state model. We have also tried the reaction using the pybox ligand complexed with ruthenium as the catalyst. Change of metal from Cu to Ru for complexation failed to increase the enantioselectivity but the diastereoselectivity was enhanced appreciably.

Chapter 2: Enantioselective Allylic Oxidation Reactions.

Enantiopure alcohols are very important structural units for synthesis of biologically active compounds. One of the possible approaches could be based on the well known Kharasch reaction, in which allylic oxidation of olefins takes place with *tert*-butyl perbenzoate in the presence of catalytic amount of copper salt. Allylic esters thus obtained could be converted into allylic alcohols by hydrolysis or reduction method. In this chapter, we have shown that copper complexes of the chiral bis(oxazolinyl)pyridine type ligands are good catalysts for allylic oxidation of olefins. The diphenyl substituted pybox ligand gave the best result. CH_3CN was a much better solvent than benzene for the reaction.

be the best. In case of cyclohexene we have achieved 81% ee which is highest, to-date, for this kind of reaction. The effect of molecular sieves was quite important in enhancing the enantioselectivity of the reaction. The high enantioselectivity in the reaction was explained based on a favourable transition state assembly in which a π -stacking of the two aromatic rings stabilizes the conformation. We get (*S*)-cyclohexenyl benzoate as the major product using (*S*)-pybox ligand. Enantioselectivity was determined based on the shift reagent study and the known rotation data. The optical induction obtained for other olefins is not very high.

Chapter 3: Enantioselective Deprotonation Reactions.

During the last four years, enantioselective deprotonation reaction of symmetrical epoxides has been studied, in great detail in our laboratory. A number of new chiral ligands have been synthesized, and ultimately a maximum of 77% ee for (*S*)-2-cyclohexen-1-ol was achieved and a series of cyclopentanoid intermediates in a maximum of 88% ee was synthesized. In this chapter, we have shown the further progress in this area. We have designed and synthesized new kinds of chiral nonracemic lithium amide bases from easily available precursor, phenylglycine. Since both the enantiomers of the precursor are available at cheap cost, the versatility of the ligands will be more. We have studied the deprotonation reaction of several epoxides. We have achieved a maximum of 80% ee in the conversion of cyclohexene oxide to (*S*)-2-cyclohexen-1-ol. We have also synthesized an enantiopure core unit in 97% ee which is very useful for prostaglandin synthesis. The latter enantioselectivity is the highest, to-date, for this kind of transformation. The enantioselectivities in all the cases were analyzed based on ^1H NMR after making the Mosher's ester.

We have also shown the development of a mild method for removal of TBDMS and THP group. Ceric ammonium nitrate (CAN) in MeOH was found to cleave them under very mild conditions. The significant feature of this reaction is that the cleavage of TBDMS ethers is catalytic in nature. The selective cleavage of TBDMS ether in the presence of THP ether and ketal group is of paramount importance, though the selectivity was found to be substrate specific to some extent. In view of the high usefulness of the TBDMS group in the organic synthesis, the present method will have a wide scope.

Chapter 4: An Approach towards Synthesis of Enantiopure Amines.

Enantiopure amines are very useful in synthetic organic chemistry. One of the approaches towards the synthesis of chiral amines is based on chiral auxiliary. In this chapter, we have shown that diphenylvalinol is a very good auxiliary for preparing 100% diastereomerically pure oxazolidines. Thus, we have prepared various pure oxazolidines. We have also tried the same with diphenylphenylglycinol. Unfortunately, these oxazolidines could not be opened with nucleophiles and we were not successful in our aim.

LIST OF ABBREVIATIONS

AcO	acetate
aq.	aqueous
bp	boiling point
BH ₃ ·DMS	borane-methyl sulfide complex
cbz	benzyloxycarbonyl
CAN	ceric ammonium nitrate
CNLA	chiral nonracemic lithium amide
m-CPBA	<i>m</i> -chloroperoxybenzoic acid
DCC	N,N'-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	3,4-dihydro-2H-pyran
DIBAL-H	diisobutylaluminum hydride
DMAP	4-N,N-dimethylaminopyridine
<i>ent</i>	enantiomer
œ	enantiomeric excess
Eu(hfc) ₃	tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium(III)
Eu(tfc) ₃	tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato], europium(III)
HOBT / HOBt	1-hydroxybenzotriazole
Im	imidazole
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
lit.	literature
mp	melting point
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
Py	pyridine
PCC	pyridinium chlorochromate
PPTS	pyridinium <i>p</i> -toluenesulfonate
r.t.	room temperature
TBDMS-Cl	<i>tert</i> -butyldimethylsilyl chloride
TLC / tlc	thin layer chromatography
THP	tetrahydropyran
TMS	tetramethylsilane
<i>p</i> -TsOH·H ₂ O	<i>p</i> -toluenesulfonic acid monohydrate
TfO	trifluoromethanesulfonate

CONTENTS

	Page No.
STATEMENT -----	i
CERTIFICATE I -----	ii
CERTIFICATE II -----	iii
ACKNOWLEDGEMENT -----	iv-v
SYNOPSIS -----	vi-viii
LIST OF ABBREVIATIONS -----	ix
 CHAPTER 1 : ENANTIOSELECTIVE CYCLOPROPANATION REACTIONS	 1-54
1. Introduction -----	2
2. Background -----	17
3. Present work -----	18
4. Experimental -----	26
5. Spectra -----	36
6. References -----	51
 CHAPTER 2 : ENANTIOSELECTIVE ALLYLIC OXIDATION REACTIONS	 55-89
1. Introduction -----	56
2. Background -----	66
3. Present work -----	67
4. Experimental -----	73
5. Spectra -----	77
6. References -----	88
 CHAPTER 3 : ENANTIOSELECTIVE DEPROTONATION REACTIONS	 90-163
1. Introduction -----	91
2. Background -----	95
3. Present work -----	96
4. Experimental -----	110
5. Spectra -----	124
6. References -----	160
 CHAPTER 4 : AN APPROACH TOWARDS SYNTHESIS OF ENANTIOPURE AMINES	 164-189
1. Introduction -----	165
2. Background -----	171

3.	Present work -----	172
4.	Experimental -----	176
5.	Spectra -----	179
6.	References -----	189
	RÉSUMÉ -----	190

CHAPTER 1

ENANTIOSELECTIVE CYCLOPROPANATION REACTIONS

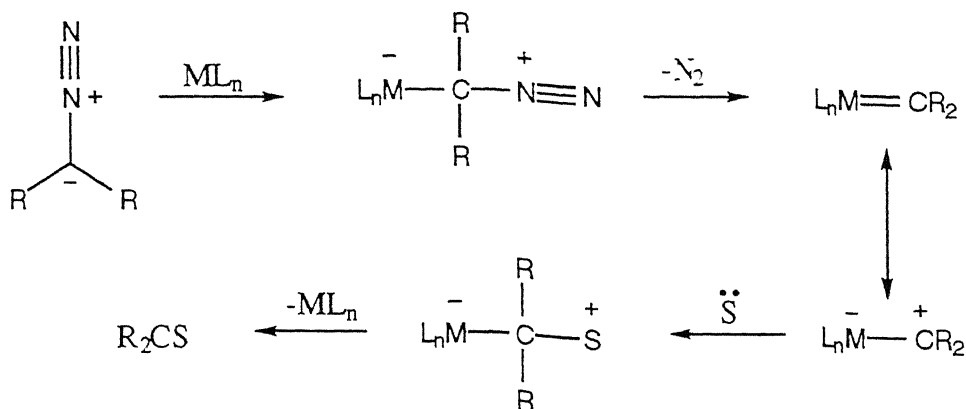
Introduction

The reaction of olefins with free carbenes or carbenoid species is called cyclopropanation reaction.¹ Since free carbenes are not useful due to their high reactivity and low selectivity, cyclopropanation reaction is usually done with carbenoid species. The term carbenoid² has been used to describe the metal-complexed intermediates formed from the decomposition of diazo compounds in the presence of transition metals and do not literally exist as a divalent carbon intermediate. Instead, these species acquire stabilization by interaction with a transition metal. Because of this interaction, metal-carbene complex is more selective in its behaviour relative to a free carbene.

The stereochemical course of these metal catalyzed reactions can be effectively controlled by appropriate organic ligands attached to the metal centre. Design and synthesis of suitable ligands, for this purpose, is a very challenging task to Organic Chemists. A number of chiral ligands, that allow a metal catalyzed process to be directed in such a way that one of the enantiomeric products is formed with a preference over the other, have been discovered during the past two decades. As a result of the development of different new transition metal catalysts and design of effective strategies for their application, synthetic uses of organic diazo compounds in asymmetric synthesis have undergone a renaissance in recent years.³ In this section we have described the literature search upto early 1996 on enantioselective cyclopropanation reactions using metal carbenoids from diazo esters. More emphasis has been given on recent aspect of the reactions. In order to have better understanding about the area, we have also described mechanistic part of the reaction in brief.

The mechanism for decomposition of diazo compounds with transition metals was, originally, suggested by Yates in 1952 (Scheme I).⁴ The nitrogen extrusion from the diazocompound is the consequence of nucleophilic attack by the diazo group onto the complex. The metal stabilized carbene then reacts with some electron-rich substrate and regenerates the catalytic species as shown in the scheme I. The ability of a transition metal to function as a catalyst is dependent upon unsaturation in the coordination sphere of the metal. Different metal complexes have been tried for this purpose and the most suitable metals are found to be Cu, Rh, Co and Ru. Among all these, copper complexes represent one of the most efficient catalysts for

cyclopropanation of olefins with diazo compounds. Diazo compounds, generally used for this reaction, are diazo carbonyl ones.

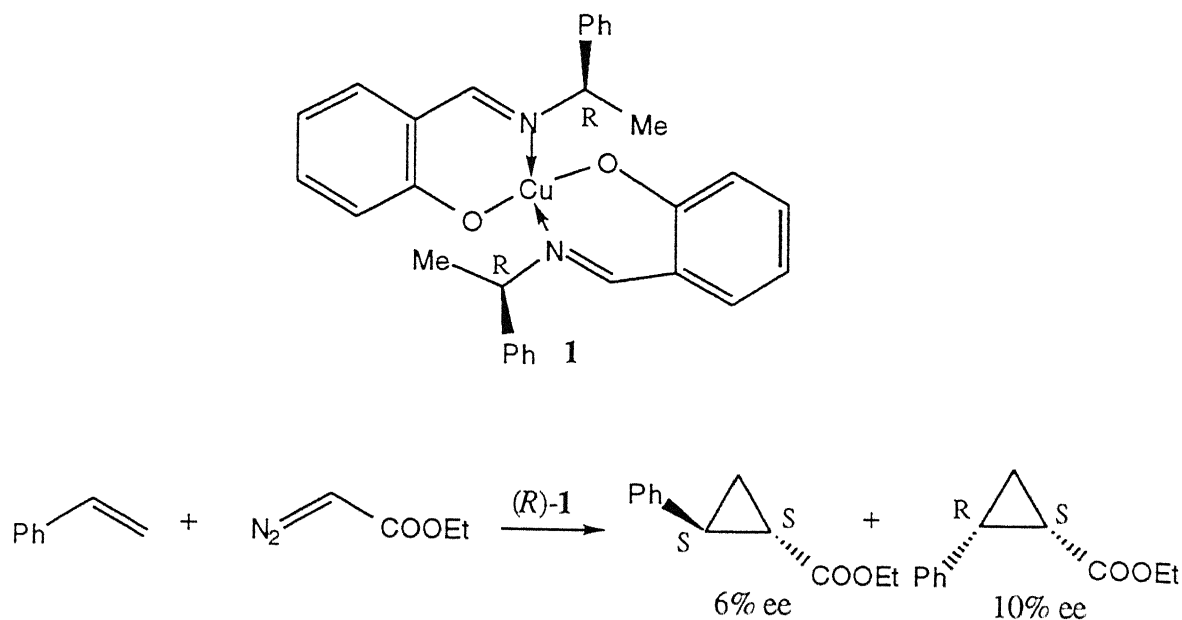


Scheme I

In 1972, Salomon and Kochi provided the basic understanding of copper catalysts in carbenoid transformations.⁵ They discovered that CuOTf is very effective for cyclopropanation reactions. Trifluoromethanesulfonate (OTf = Triflate) like perchlorate is an extremely weak coordinating anion and metal salts such as those of Cu (I) and Cu (II) are extremely ionized even in nonaqueous solution. So, the electrophilic metal ion is capable of multiple coordination which makes the cyclopropanation process very facile. They also showed that the catalytically active species is Cu (I), and not Cu (II). Since CuOTf is relatively difficult to handle, Cu(OTf)₂ is generally used as a precursor which gets reduced *in situ*.⁵ The authors also inferred that the reduction of Cu (II) to Cu (I) took place more readily by diazomethane but less readily by ethyl diazoacetate. It was difficult to carry out the mechanistic study of the reaction in detail because most of the Cu (I) complexes, in solution, undergo disproportionation to Cu (0) and Cu (II). It is well established that the coordination of Cu(I) with various ligands inhibit disproportionation to a great extent. Kochi has also shown that the rate of diazo compound decomposition is inversely proportional to the concentration of the olefin. The inverse dependence is meaningful only in the concentration range above 1M.⁵ In the absence of alkene, ethyl diazoester decomposes to diethyl maleate, fumarate and other higher esters.

Catalytic asymmetric cyclopropanation was first reported in 1966 by Nozaki *et al.*^{2,6} They used chiral schiff-base-copper (II) complex **1** to catalyze the reaction of diazo compounds with olefins.

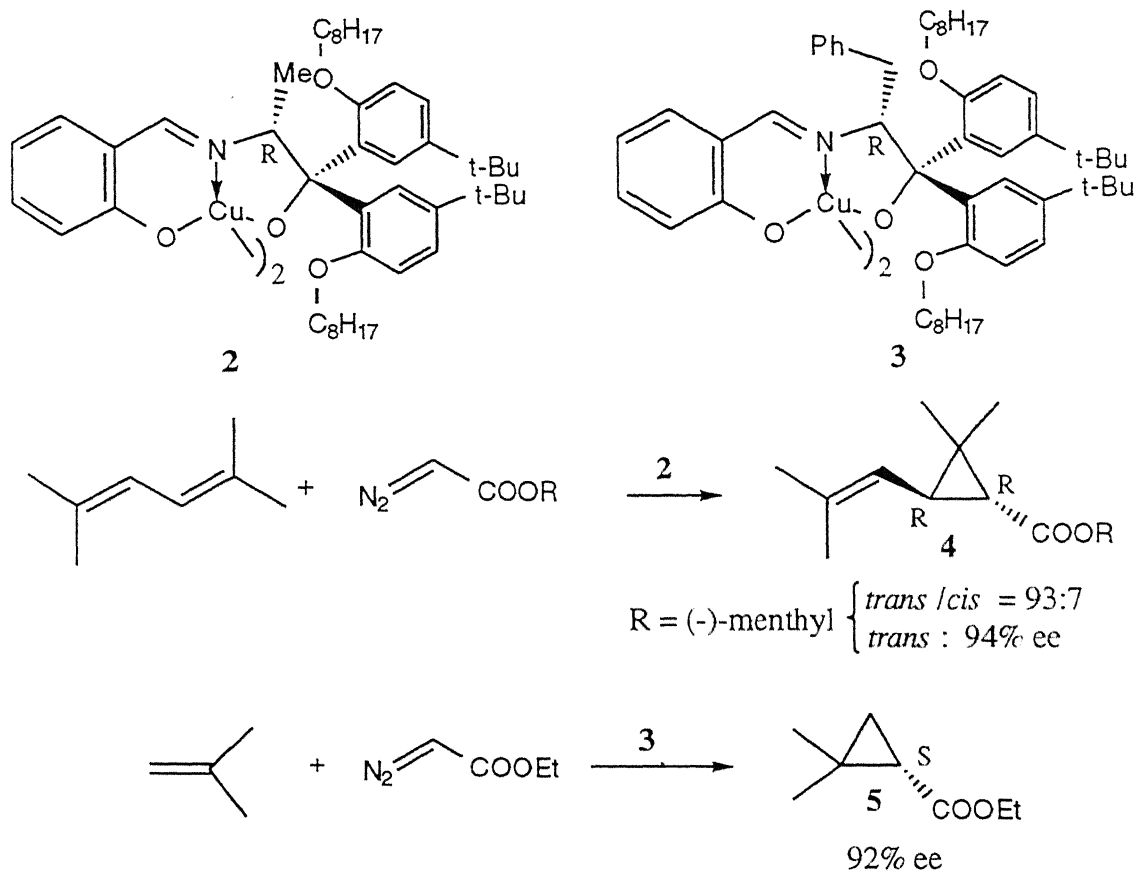
diazoacetate to give the products, *trans*- and *cis*-2-phenylcyclopropanecarboxylic esters (Scheme II). Although the enantioselectivity was very poor (below 10% ee), the stage was set for further development in the area.



Scheme II

Later, Aratani and coworkers reported dramatic improvement in optical yield after extensive screening of salicylaldehyde ligands.⁷ The ligands were prepared from salicylaldehyde and amino alcohols derived from α -amino acids; alanine and phenyl alanine turned out to be more appropriate.⁸ The air-stable copper chelates (**2** & **3**) were prepared by treating the Schiff bases with cupric acetate followed by sodium hydroxide. These chelates were shown to have a dimeric structure. The chiral Cu (II) complex **2** gave 80% ee for the *trans*-isomer during the cyclopropane formation from styrene and (-)-menthyl diazoacetate. A natural chrysanthemic acid derivative **4** [*trans*-(+)-1*R*,2*R* isomer] was synthesized upto 94% ee by reaction of 2,5-dimethyl-2,4-hexadiene and (-)-menthyl diazoacetate using the catalyst **2**.⁷ The enantioselectivity in the above reaction drops down to 68% if ethyl diazoacetate was used in the reaction. Similar effect on diastereoselectivity of the reaction was also seen. The bulkier 'R' group gave higher ratio of *trans*-isomer. The Cu (II) complex **2** has also been used in synthesis of other potent units of pyrethroid insecticides and biologically active compounds.⁷⁻⁹ The catalyst **3** has been used on an industrial

scale for the cyclopropanation of 2-methyl-1-propene with ethyl diazoacetate to provide ethyl (*S*)-2,2-dimethylcyclopropanecarboxylate **5** in 92% ee.⁷



Scheme III

Camphor derived ligands have also been introduced for enantioselective cyclopropanation reactions, however, they did not become popular because of certain limitations.^{10,11}

After the discovery by Teyssie and coworkers¹² that rhodium (II) carboxylates facilitate nitrogen loss from diazo compounds, a lot of work has been done using chiral rhodium catalysts. Rh₂(OAc)₄ has emerged as the most effective catalyst for carbenoid transformations. It is a binuclear compound with four bridging acetate ligands and has one vacant axial coordination site per metal atom. Early work by Brunner¹³ and McKervy¹⁴ on cyclopropanation reaction of styrene with ethyl diazoacetate using chiral rhodium complexes, prepared from enantiopure carboxylic acids (R₁R₂R₃CCOOH), gave very poor enantioselection (below 12% ee). Further modifications in the same ligand system did not improve the result.¹⁵ It has been pointed out that

the poor enantioselectivity could be due to larger distance of asymmetric center from the carbenoid in the metal carbene intermediate.¹⁶

Doyle and coworkers introduced several chiral rhodium (II) carboxamides of the type **6** (Fig. 1) for cyclopropanation reactions.¹⁷ These were constructed to allow placement of a chiral attachment at nitrogen close to the reactive carbene center. In view of less reactivity of these towards diazo compounds and having chiral center close to the carbenoid center, better enantioselectivity was expected in the cyclopropanation reaction.

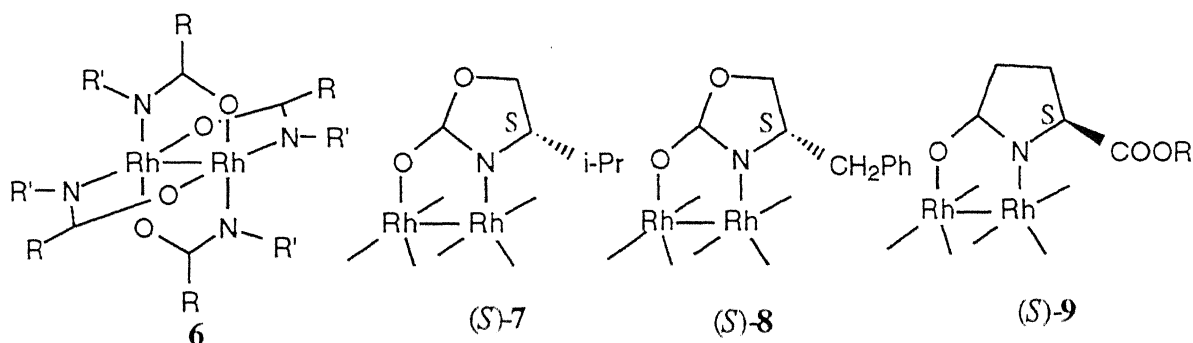
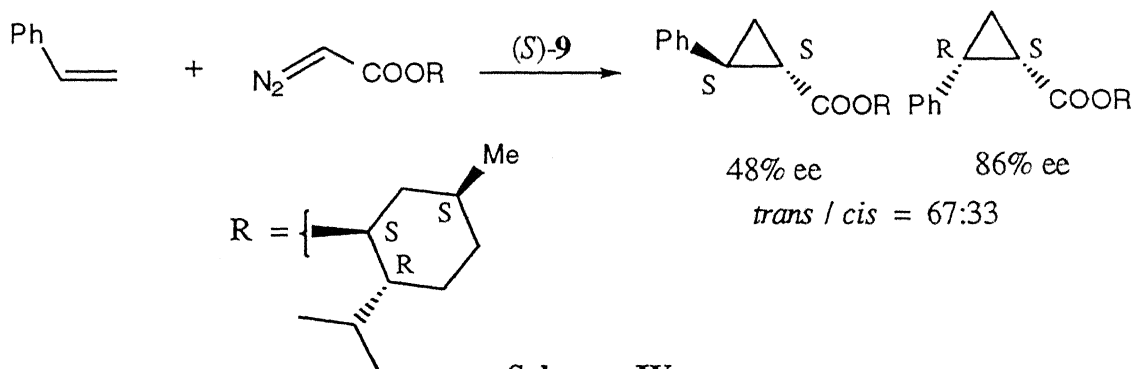


Figure 1

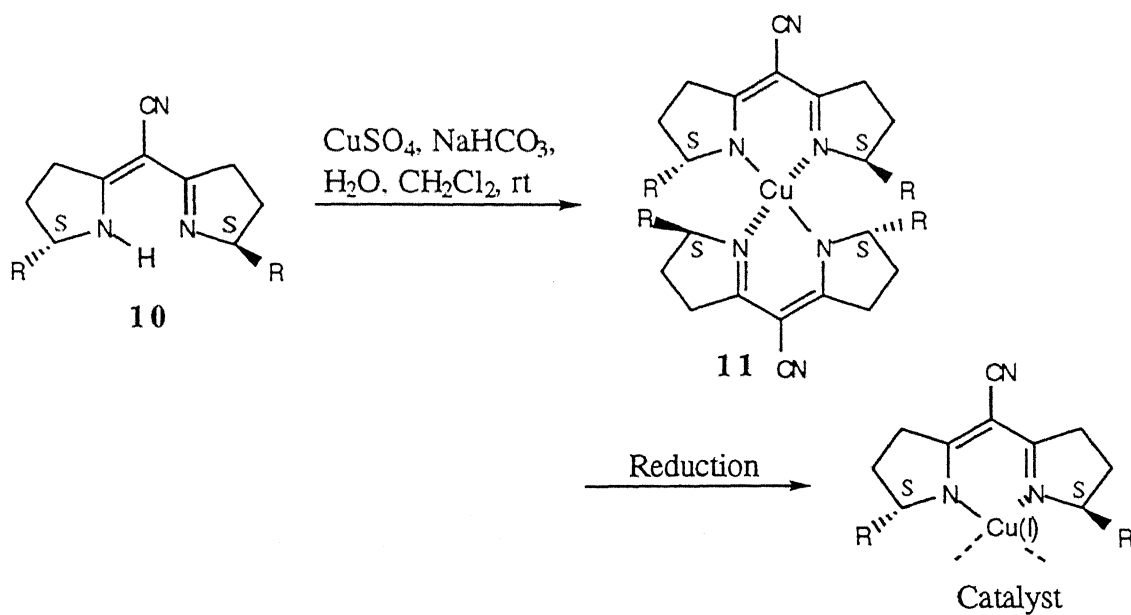
The catalysts **7 - 9** were prepared from $\text{Rh}_2(\text{OAc})_4$ by ligand exchange with the corresponding oxazolidones and pyrrolidones in refluxing chlorobenzene. These catalysts, in general, are different from previous chiral copper catalysts in the sense that %ee's for the *cis*-cyclopropane derivative from reactions with styrene are greater than those for the *trans*-isomers.



Scheme IV

The catalyst **9** is superior to the catalysts **7** & **8** in inducing asymmetric induction in the cyclopropanation reaction of styrene with *l*- and *d*-menthyl diazoacetate. The rhodium catalyst (*S*)-**9** gave a maximum of 86% ee for the *cis*-isomer and 48% ee for the *trans*-isomer in the above cyclopropanation reaction with *d*-menthyl diazoacetate (Scheme IV). The diastereoselectivity in the reaction is moderate. Recently, the catalyst **9** has been used in enantioselective cyclopropanation reaction where very high asymmetric induction (94% ee) was obtained.¹⁸

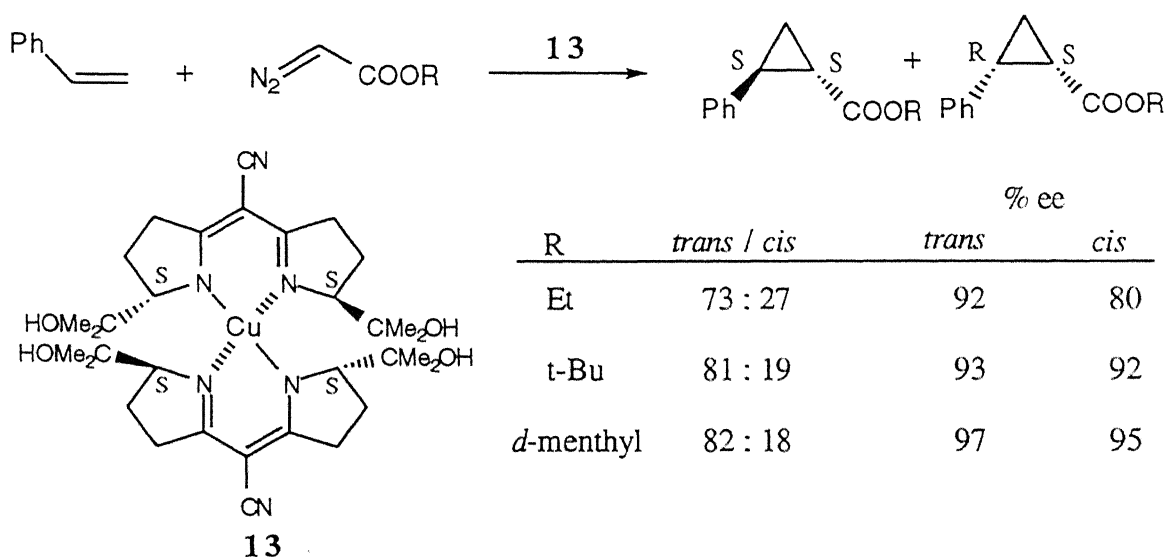
The most significant contribution in the development of chiral copper catalyst came from Pfaltz and coworkers with his report in 1986 on semicorrin type ligands **10** for enantioselective cyclopropanation reaction.¹⁹ The semicorrin structure is characterized by a vinylogous amidine system and the name 'semicorrin' was originally given by Stevens *et al.*²⁰ The geometry of the semicorrin ligands **10**, which were easily synthesized from commercially available (*S*)- and (*R*)-pyroglutamic acid, is ideal for coordinating metal ions. Its *C*₂-symmetry has a favourable effect on stereoselectivity as it restricts the number of competing diastereomeric transition states. The Cu(II) complexes were synthesized as shown in scheme V.²¹ The violet bis-(semicorrinato) complex **11** was characterized by X-ray analysis. The metal center of **11** is almost shielded by the two ligands. Therefore, this type of complex was not expected to exhibit any useful catalytic activity unless one of the two semicorrin ligands dissociates from the coordination sphere.



Scheme V

In fact, the actual catalyst in the cyclopropanation reaction is Cu (I) species **12** which is produced *in situ* as a yellow-brown solution through reduction of **11** by ethyl diazoacetate at 85 °C for few minutes. Treatment of the Cu (II) complex **11** with phenylhydrazine at room temperature also produced the same catalytic species. Alternatively, the catalyst **12** could also be generated by treating the free ligand **10** with Cu (I)-*tert*-butoxide.

A variety of Cu (II) complexes, by changing the 'R' in the semicorrin ligand **10**, were tested on styrene for cyclopropanation reaction. The highest selectivities were obtained with **13** when 'R' is bulky, such as C(Me)₂OH. The results are summarized in scheme VI. A maximum of 97% ee was obtained for *trans* product and 95% ee for the *cis* one using *d*-menthyl diazoacetate. The relatively poor *trans* /*cis* selectivity in the cyclopropanation of terminal olefins is a general problem and it is observed with other catalysts as well. Here, the ratio is independent of the catalyst structure, but it increases if ethyl diazoacetate is replaced by sterically more demanding diazo esters. Aza-semicorrins gave equally high enantioselectivity in the cyclopropanation of styrene.²¹



Scheme VI

Pfaltz's catalyst is not suitable for trisubstituted olefins. For example, the complex **13** gave only 33% ee for the chrysanthemic acid derivative. In fact, Aratani's catalyst is better than Pfaltz's catalyst for the synthesis of Chrysanthemic acid type derivatives. (semicorrinato) Copper catalysts have also been employed for 1,2-*trans*-disubstituted olefins with diazomethane (70-75% ee).

The enantioselectivity obtained with Pfaltz's catalysts has been explained using a suitable model as shown in Figure 2. The electrophilic copper carbenoid carbon atom is attacked by the more nucleophilic end of the olefin. Depending on the direction of attack, the ester group at the carbenoid center either moves forward or backward. In the approach **b**, a repulsive steric interaction builds up between the ester group and the substituent 'R' whereas the approach **a** does not face this kind of interaction. Thus, the pathway **a** is favoured over pathway **b**. The model also explains that the *trans* / *cis* selectivity is determined by the structure of the olefin and diazo compounds only, and not by the semicorrin ligand.

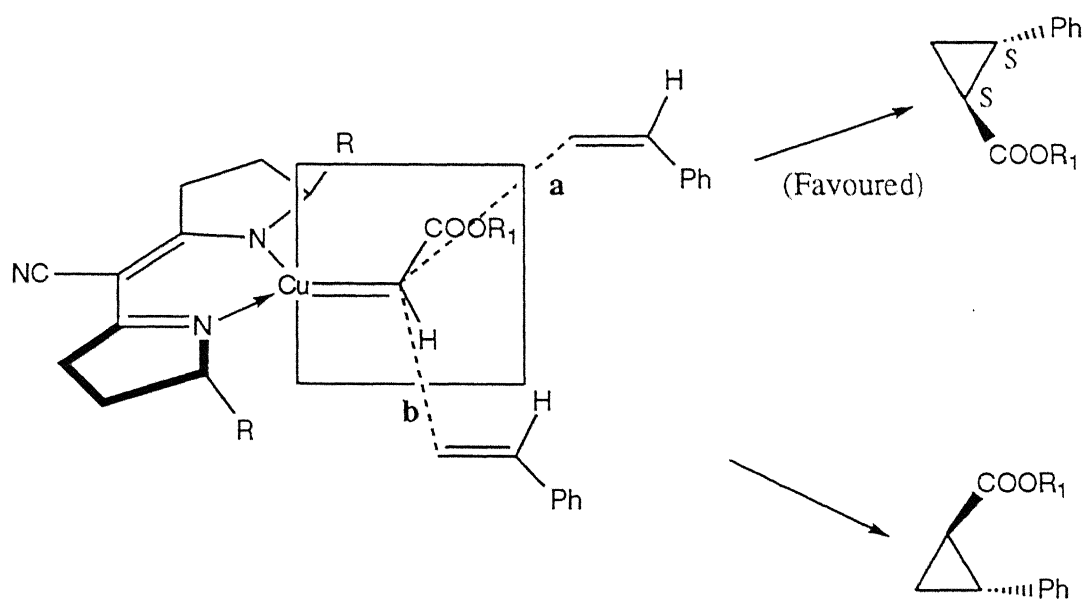
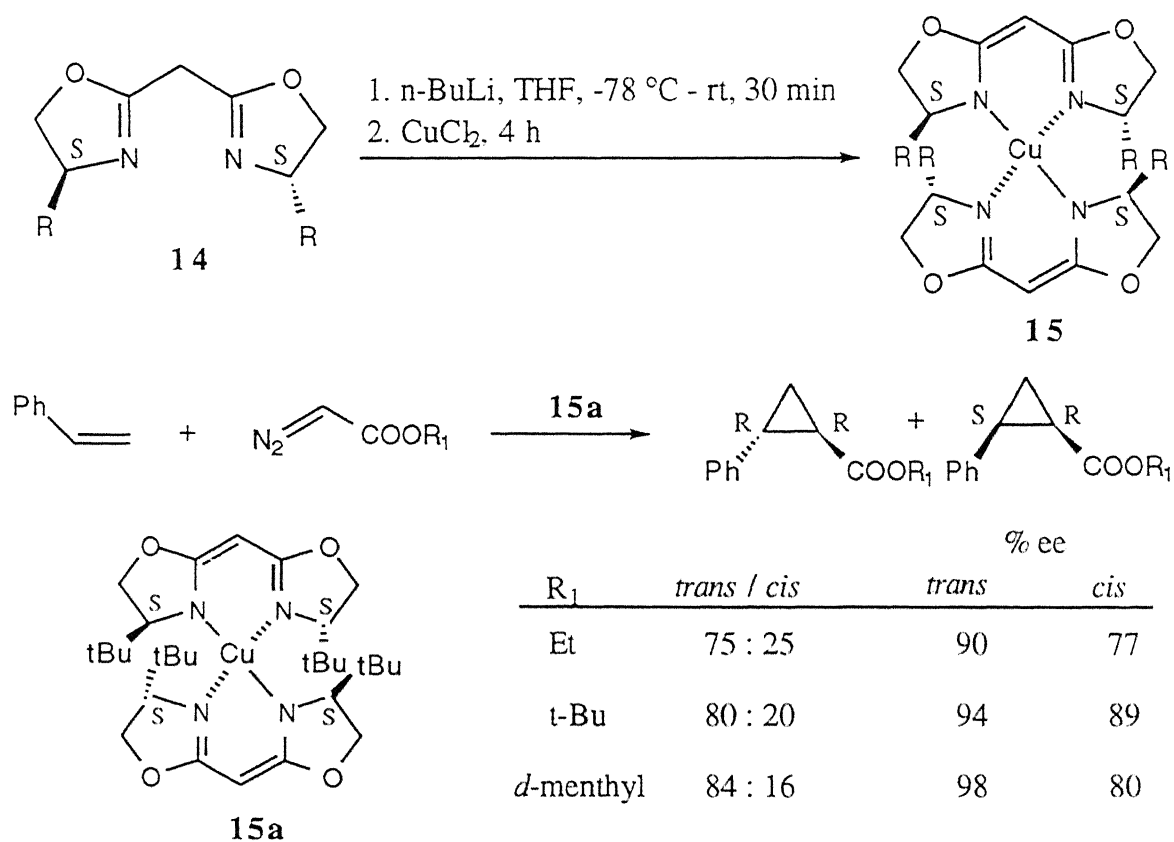


Figure 2

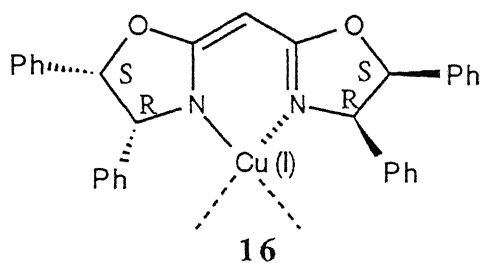
In 1990, Masamune and coworkers²² prepared several bis-oxazoline ligands **14** from the corresponding aminoalcohols and diethyl malonate. These ligands were converted into their violet Cu(II) complexes **15**. Treatment of the complexes with phenylhydrazine provided the active catalytic Cu (I) species which were evaluated, *in situ*, for enantioselective cyclopropanation using ethyl diazoacetate and styrene in the standard fashion. As the size of the R group in the ligand is enlarged, both diastereoselectivity and enantioselectivity increased. Among several complexes tried, the complex **15a** in which R is *tert*-butyl group gave the best results; 90% ee for the *trans*-isomer and the 77% ee for the *cis*-isomer (Scheme VII). The enantioselectivities for both *trans* and

cis products are affected by the R₁ group of diazoacetate. *d*- and *l*-menthyl diazoacetate gave better results than ethyl or *t*-butyl diazoacetates as depicted in the scheme VII.

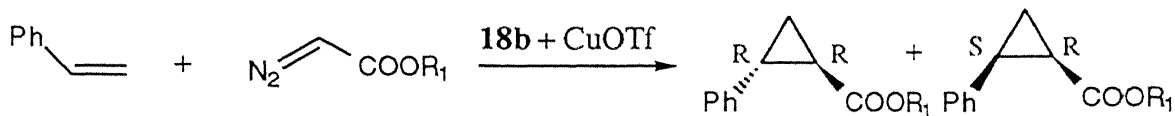
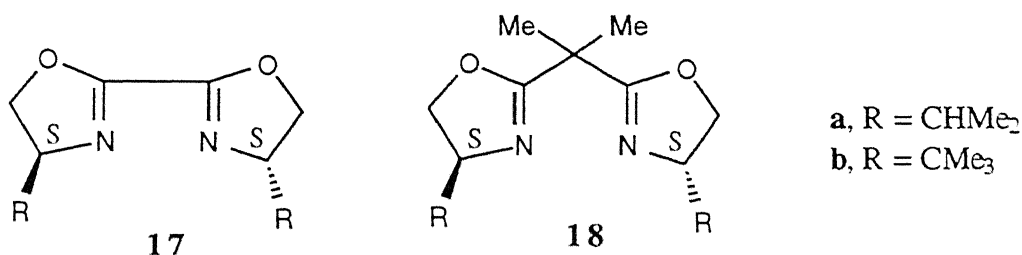


Scheme VII

Masamune in his subsequent paper²³ modified the bis-oxazoline ligands for enantioselective cyclopropanation of trisubstituted olefins. Thus, chrysanthemate derivative **4** (R = dicyclohexyl methyl) was synthesized in a maximum of 94% ee (*trans-cis* ratio = 95:5) using dicyclohexyl methyl diazoacetate in the presence of the catalyst **16**. *l*-Menthyl diazoacetate gave 92% ee (*trans-cis* ratio = 92:8) for the **4** (R = menthyl). The dicyclohexyl methyl group has the advantage in terms of its removal by acidic or basic reagents. Unfortunately, the catalyst **16** gave very poor optical induction (26% ee for the *trans*- and 20% ee for the *cis*-products) for the cyclopropanation of styrene.



Similar contemporary work was reported by Evans and coworkers²⁴ in early 1991. They developed a series of chiral bis-oxazoline ligands **14**, **17** and **18** which formed 1:1 complex with CuOTf. The complexes, thus derived, were evaluated for cyclopropanation reaction of styrene. Under the conditions where **18b** gave 99% ee using ethyl diazoacetate, valine based ligand **18a** gave only 49% ee. Using the ligand **18b**, they found out that sterically demanding diazoacetates increase the diastereoselectivity without having much effect on the enantioselectivity. The *trans/cis* ratio (94:6) and enantioselectivity (99%) for cyclopropyl esters were maximum in case of diazoacetic ester derived from 2,6-di-*tert*-butyl-4-methylphenol (BHT) as shown in scheme VIII.



R ₁	<i>trans</i> / <i>cis</i>	% ee	
		<i>trans</i>	<i>cis</i>
Et	73 : 27	99	97
t-Bu	81 : 19	96	93
BHT	94 : 06	99	-

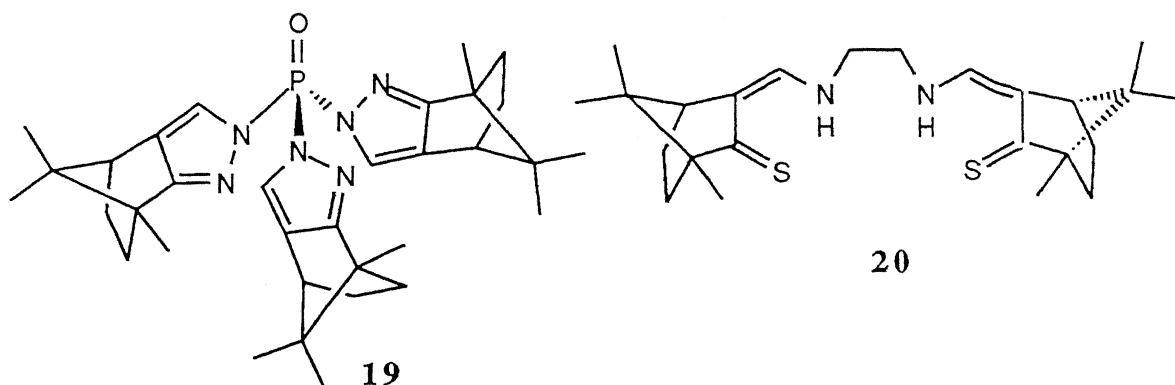
Scheme VIII

The lower enantioselectivity (3% ee for *trans* and 8% ee for *cis*) with the ligand **17** suggested that six-membered chelates, formed after complexation with CuOTf, were preferred than five-membered ones for effective catalysis. Copper (II) triflate complexes did not catalyze the cyclopropanation reaction unless they were heated to 65 °C in the presence of ethyl diazoacetate or activated with phenylhydrazine. Other Cu (I) and Cu (II) salts such as halides, cyanide, acetate, and perchlorate showed little or no catalytic activity with very poor enantioselection.

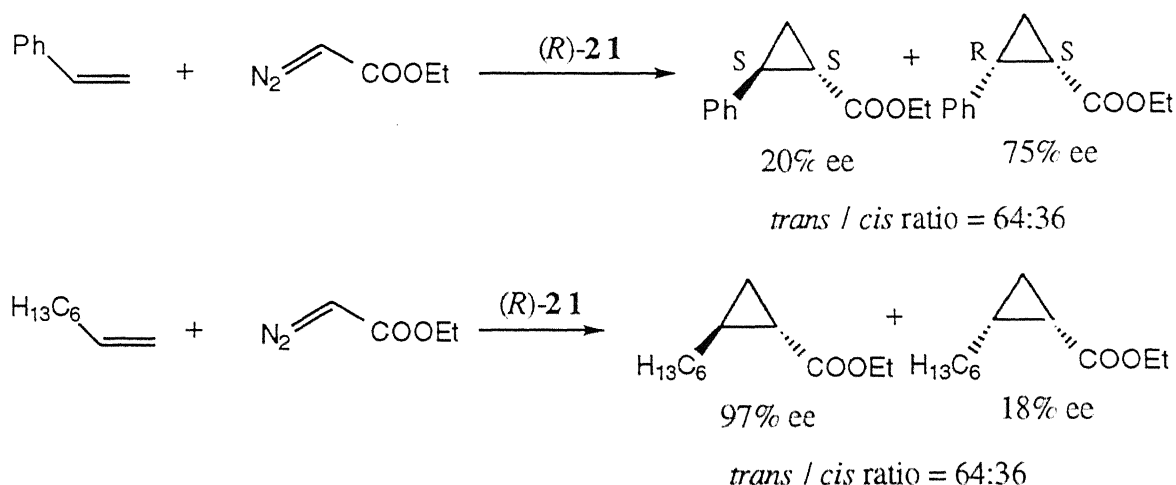
Evans *et al.* succeeded in getting a crystal structure of the complex of **18b** and CuOTf.²⁵ The X-ray crystal structure shows a single stranded helical polymer with three fold symmetry where the ligand occupies a bridging position between two linear, two-coordinate Cu(I) ions. The structure further reveals that the triflate counterion is dissociated from the metal center. In solution the polymeric structure is disrupted; the ligand is coordinated to the copper atom and is undergoing rapid ligand redistribution. The triflate ion remains fully dissociated from the metal center.

The stereochemistry for the *cis*-cyclopropyl ester had been misassigned by Masamune, and later on, it was rectified in the Evans's paper that the configuration at C-1, i.e., the carbon attached to the carboxylic ester group remains the same in major enantiomers of *trans* and *cis* compounds. The major *cis* diastereomer should be (1*R*, 2*S*) as already corrected in the scheme VII.

Tolman and coworkers²⁶ introduced enantiomerically pure copper (I) complex of a C₃-symmetric polypyrazole ligand **19** in the asymmetric cyclopropanation reaction of styrene. Although the ligand was novel, the asymmetric induction in the reaction was poor (31% ee for *trans* and 51% ee for *cis* cyclopropyl ethyl esters).

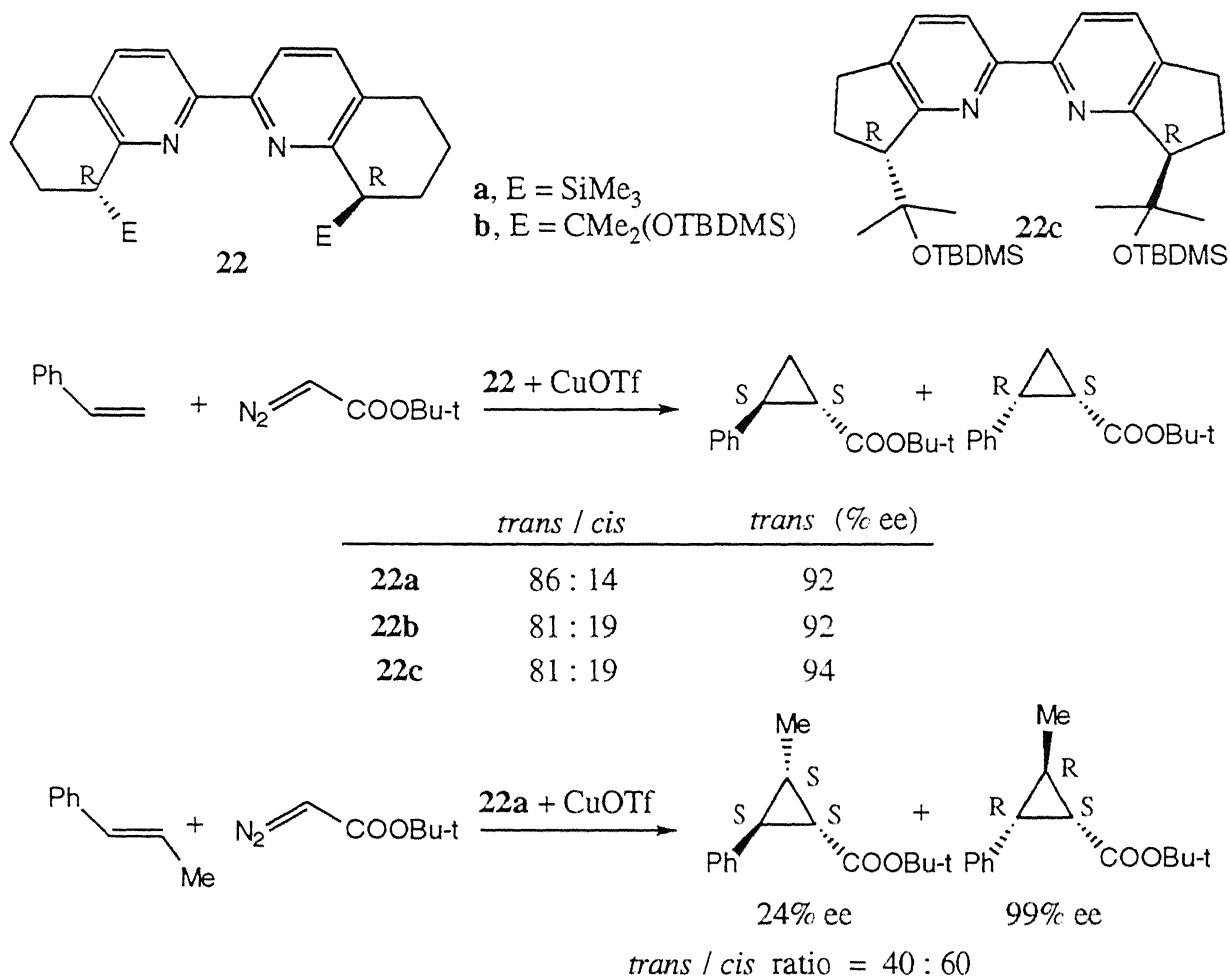


Recently, a cobalt (II) complex (*R*)-**21** of the ligand **20** was prepared²⁷ using Cobalt (II) dichloride hexahydrate to study the cyclopropanation reaction of styrene and 1-octene with ethyl diazoacetate. The results (Scheme IX) in terms of enantioselectivity are opposite for styrene (75% ee for the *cis*-isomer) and 1-octene (97% ee for the *trans* isomer). Copper (II) complex of the same ligand **20** gave poor asymmetric induction (35 - 45%) in the cyclopropanation reaction.



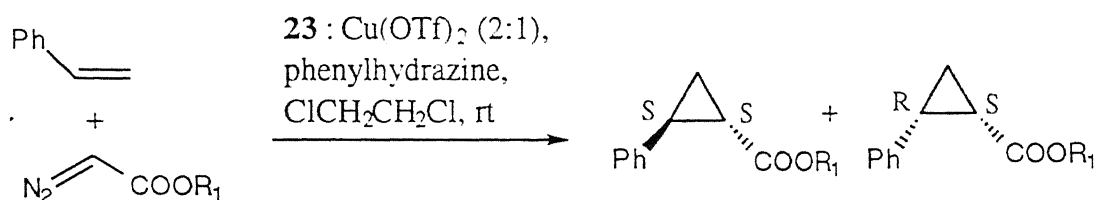
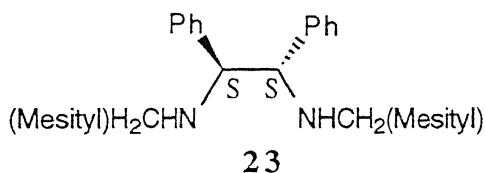
Scheme IX

Ito and Katsuki²⁸ examined cyclopropanation of styrene and other alkenes using a complex of optically active bipyridine ligands and CuOTf. Some of the results with selected ligands **22** are summarized in scheme X. Styrene derivatives bearing electron withdrawing group showed higher enantioselectivity than those with electron donating group, suggesting the participation of electrophilic copper carbene species in this reaction. A very high asymmetric induction (99%) has been observed for major *cis* isomer in the reaction of *trans*- β -methyl styrene (Scheme X). This result is different from that with bis-oxazolines. Katsuki has explained the reaction using the Pfaltz's proposal. The facial approach of the *trans*- β -styrene is same but the conformational orientation is different. In another study,^{28e} he had used the salen based ligands complexed with cobalt for the enantioselective cyclopropanation reaction.



Scheme X

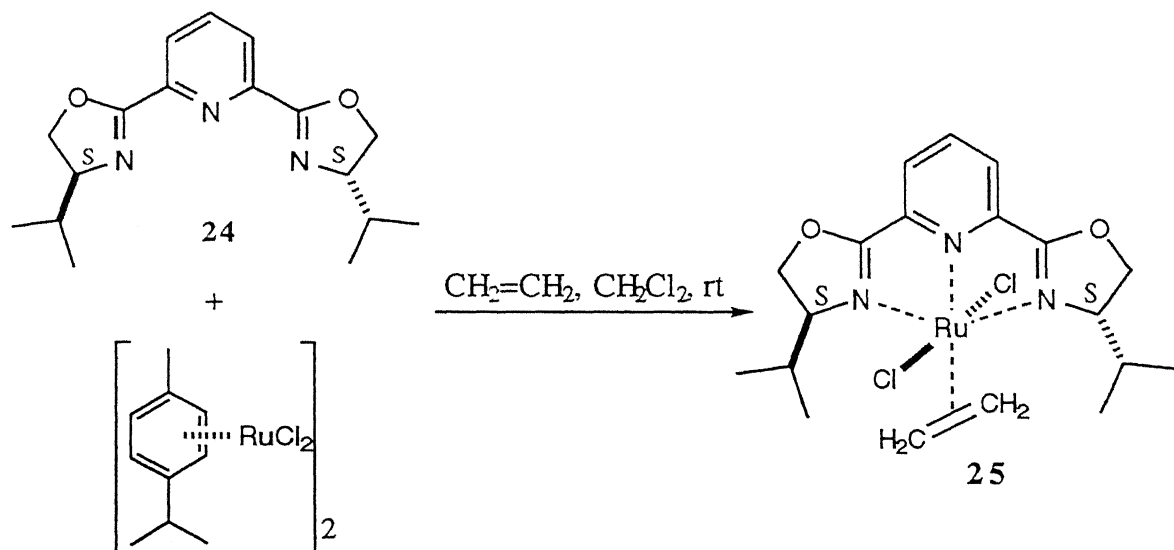
In a recent paper,²⁹ it has been reported that a C₂-symmetric diamine 1,2-ligand **23** when mixed with equimolar amount of Cu (OTf)₂, forms a paramagnetic blue complex (mp 158-160 °C), which becomes diamagnetic, on treatment with phenylhydrazine (colour changed from blue to orange). The resulting orange solution showed a high catalytic activity in the reaction of styrene with ethyl diazoacetate. The asymmetric induction in this reaction was poor (24% ee for the *trans* isomer of the 2-phenyl-1-cyclopropanecarboxylate ester). It was also reported that on using 2 equivalent of the diamine **23** with respect to Cu(OTf)₂, a diamagnetic colourless complex (mp 243-244 °C) was produced from the blue solution and it showed higher catalytic and higher enantioselectivity in the same reaction (Scheme XI). This method was applied in the synthesis of naturally occurring enantiomer of chrysanthemic acid derivative **4** using *l*-menthyl diazoester. The major product (*trans*-*cis* ratio = 88:12) was obtained in 74% ee.



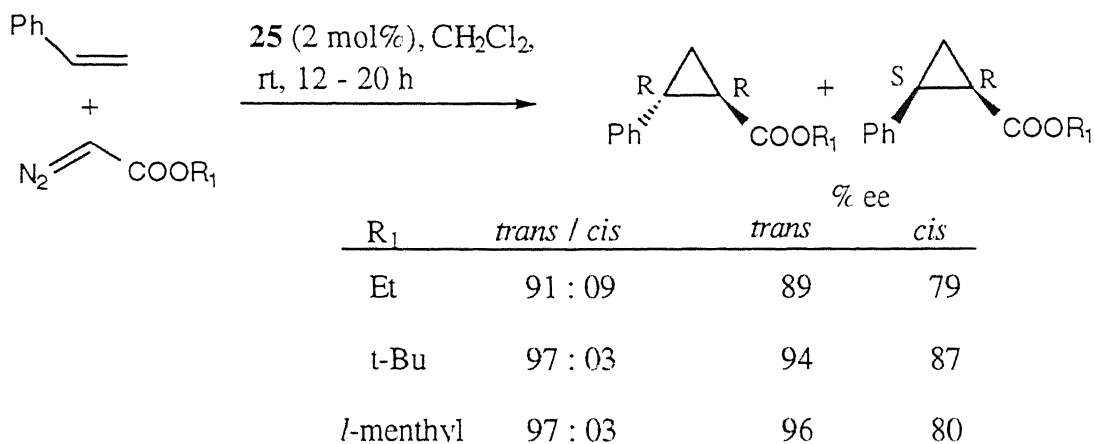
R ₁	<i>trans</i> / <i>cis</i>	% ee	
		<i>trans</i>	<i>cis</i>
Et	74 : 26	86	58
<i>t</i> -Bu	83 : 17	72	-
<i>l</i> -menthyl	91 : 09	94	-

Scheme XI

Nishiyama and coworkers³⁰ recently reported that ruthenium complex of bis(oxazolinyl)pyridine **24** was an excellent catalyst for asymmetric cyclopropanation reaction of styrene and some other olefins. As high as 96% ee for the *trans* product from styrene was reported (Scheme XII).

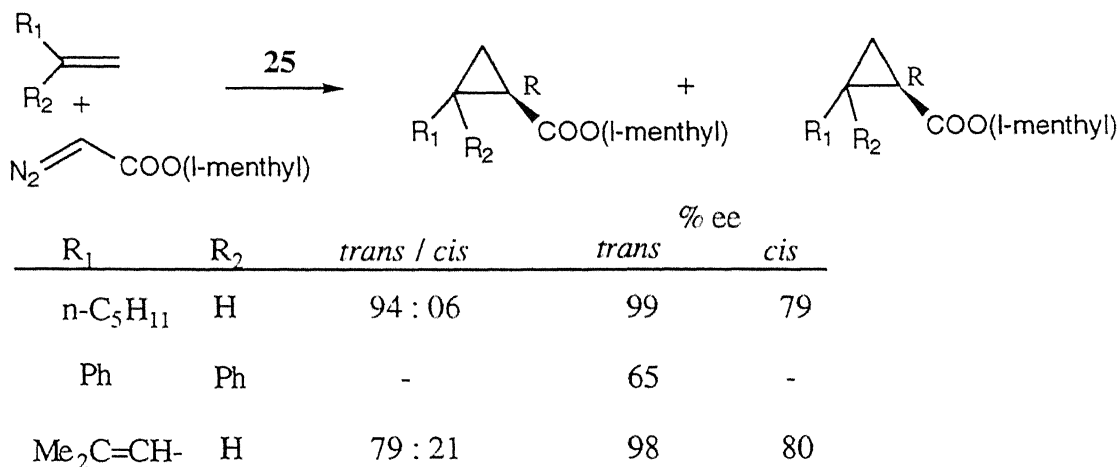


The catalytic efficiency of the catalyst **25** is very high as even 1 mol % of the **25** gave the same level of enantioselection in the reaction.



Scheme XII

Other olefins such as 1-heptene, 1,1-diphenylethylene, and 4-methyl-1,3-pentadiene, on cyclopropanation with **25** and *l*-menthyl diazoacetate under the same conditions, gave high % ees upto 99% (Scheme XIII). The drawback with this catalyst is that β -methylstyrene and 2,5-dimethyl-2,4-hexadiene failed to undergo cyclopropanation reaction.



Scheme XIII

In view of the above literature search we started the work in 1992 and the results are summarized in the following section.

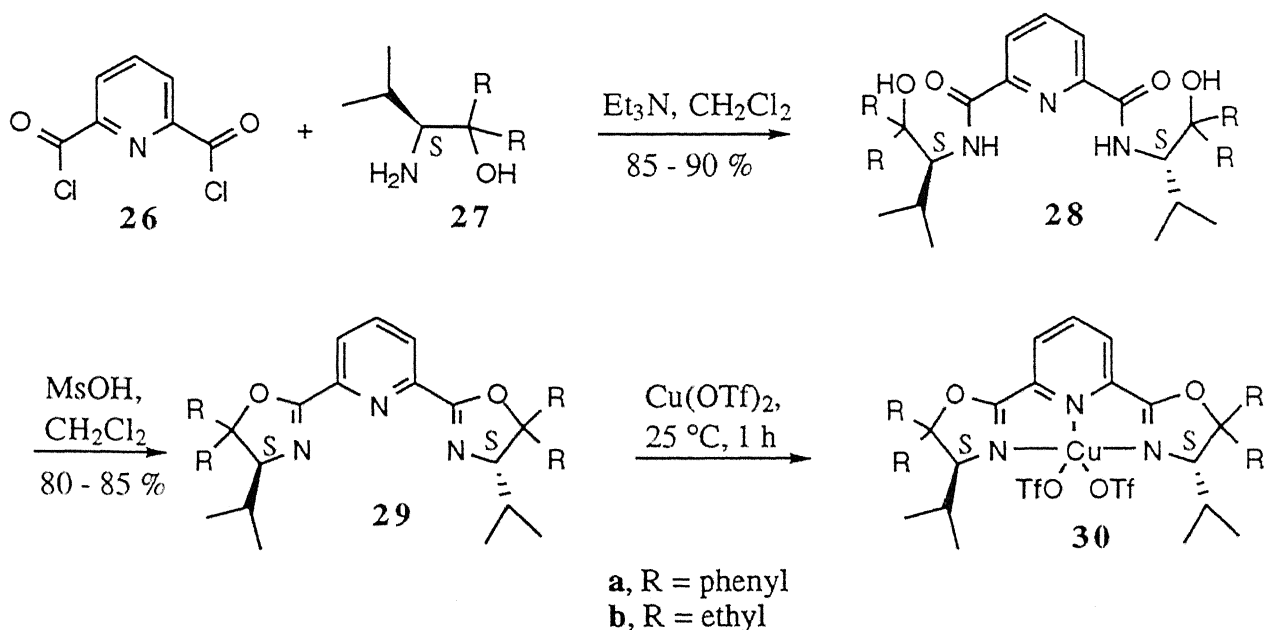
Background

Asymmetric cyclopropanation of alkenes was successfully carried out in the last thirty years using different transition metal complexed ligands as catalysts. Good to high enantioselectivities have been achieved in a variety of alkenes. In the preceding chapter we have seen that, after the first example of enantioselective cyclopropane formation reported by Nozaki,^{2,6} tremendous amount of work has been done in this area. Copper complexes of semicorrin type ligands of Pfaltz^{19,21} and bis (oxazoline) type ligands of Masamune^{22,23} have given remarkable results. As a consequence of our interest in asymmetric synthesis area,³¹ we introduce here bis(oxazoliny)pyridine (pybox) type ligands for enantioselective cyclopropanation reactions.

Chiral rhodium pybox complexes had been extensively used by Nishiyama and co-workers in asymmetric hydrosilylation³² and dehydrogenative silylation of ketones.³³ The same type of ligand had also been used in chiral recognition of 1,1'-bi-2-naphthol.³⁴ Molecular model of this type of ligands around Cu metal looked comparable with Evans's ligand and, to the best of our knowledge, this had not been used for asymmetric cyclopropanation reaction.^{35,36} In this chapter we describe our efforts towards synthesis, application, and some mechanistic study with these chiral nonracemic pybox type ligands.

Present Work

We envisioned that a chiral nonracemic pybox type ligand **29** might be quite suitable for inducing chirality in a cyclopropanation reaction. We were mainly interested in the ligand **29a** which had four phenyl groups. The presence of phenyl groups would make the ligand hydrophobic in nature and it would be easy to purify by column chromatography. The ligands **29** were synthesized in two steps, viz., by coupling of 2,6-dipicoyl chloride **26**³⁷ and aminoalcohols **27**³⁸, followed by intramolecular condensation³⁹ using methanesulfonic acid under azeotropic removal of water (Scheme XIV). Its reaction with stoichiometric amount of Cu(OTf)₂ in (CH₂)₂Cl₂, CH₂Cl₂ or CHCl₃ led to the formation of a blue-green colour complex. The Cu(II) complex of **29a** was isolated as a solid, but unfortunately we could not get its crystal structure. So we assume its structure as **30** (monomeric form). The cyclopropanation reaction was carried out on olefins using diazoester and 1 mol % of Cu(II)-complex **30**, prepared *in situ*, in chlorinated solvents.



Scheme XIV

The cyclopropanation reactions of styrene and alkyl diazoacetates were carried out in CHCl₃ using 1 mole percent of Cu(II) complex as catalyst, made *in situ*. In our initial study, we

used ethyl and *tert*-butyl diazoacetates for the cyclopropanation of styrene. The cyclopropanated products **31** and **32** were obtained in high yield. Results show that change of 'R' group from phenyl to ethyl has very little effect on the diastereoselectivity and enantioselectivity. Use of bulkier diazoacetate brings about the increase in both diastereoselectivity and enantioselectivity (Table 1). This observation is in accord with the literature work.

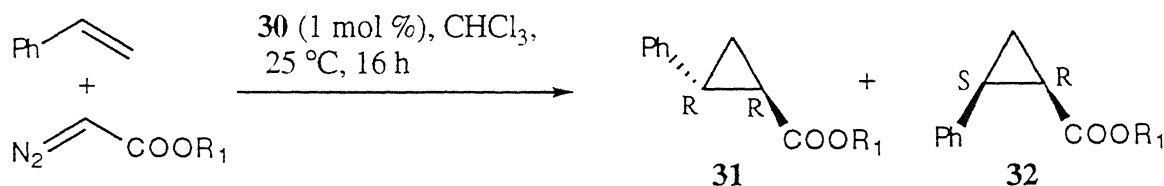


Table 1. 'Asymmetric Cyclopropanation Reaction of Styrene with Catalysts **30**'

Catalysts	R ₁	<u>Diastereoselectivity</u> ^a trans : cis	<u>Enantioselectivity</u> ^b		<u>Yield</u> ^c (%)
			trans	cis	
			% ee	% ee	
30b	Ethyl	64 : 36	26	0	86
30b	<i>t</i> -butyl	70 : 30	33	0	95
30a	Ethyl	66 : 34	28	8	93
30a	<i>t</i> -butyl	70 : 30	35	6	80

^aDetermined by ¹H-NMR spectrum. ^b% Ee was determined by 400 MHz ¹H NMR spectrum of corresponding methyl esters with Eu(tfc)₃ shift reagent. ^cYield is for mixture of cis and trans compounds.

Using **30a** as the catalyst, we carried out the cyclopropanation reaction of styrene with *tert*-butyl diazoacetate in different solvents at different temperatures. The results are summarized in table 2. Chloroform was a better solvent than dichloromethane and dichloroethane. Lowering the temperature to 0 °C from r.t. decreased both the yield and selectivity. The enantioselectivity in the case of styrene using the catalysts **30** was not encouraging. We applied the catalyst **30a** for the cyclopropanation of other different olefins such as α-methylstyrene, 1-decene, and 2,5-dimethyl-2,4-hexadiene. The last substrate was important because its cyclopropanated product gives the ester of chrysanthemic acid which is an acid component of pyrethroid, an insecticide of high activity and low mammalian toxicity. The preliminary rotation data indicated that these substrates

also gave poor enantioselectivity (Table 3). In view of the low rotation data, the enantiomeric excesses in these cases were not determined accurately.

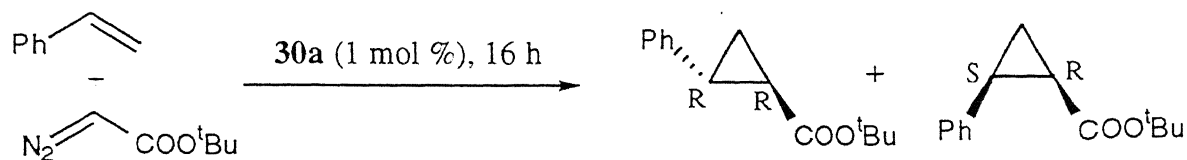


Table 2. 'Asymmetric Cyclopropanation Reaction of Styrene with t-Butyl diazoacetate using a Catalyst 30a Under Different Conditions'

Solvent	Temp.	Diastereoselectivity ^a trans : cis	Enantioselectivity ^b		Yield ^c (%)
			trans % ee	cis % ee	
CHCl ₃	r.t.	70 : 30	35	6	80
CHCl ₃	0 °C	64 : 36	20	24	48
CH ₂ Cl ₂	r.t.	57 : 43	12	0	82
ClCH ₂ CH ₂ Cl	r.t.	70 : 30	23	5	77

^aDetermined by ¹H-NMR spectrum. ^b% Ee was determined by 400 MHz ¹H NMR spectrum of corresponding methyl esters with Eu(tfc)₃ shift reagent. ^cYield is for mixture of cis and trans compounds.

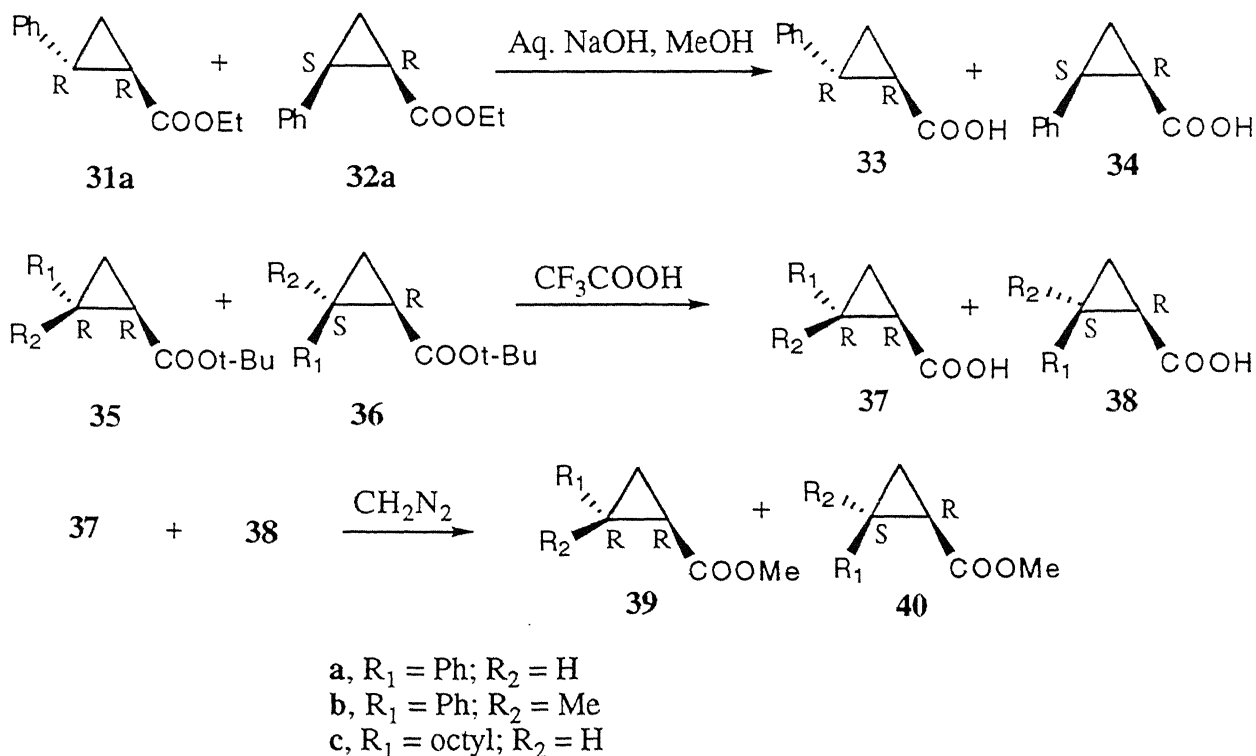
Table 3. 'Asymmetric Cyclopropanation Reaction of Different Olefins with t-Butyl diazoacetate using the Catalyst 30a'

Olefins	Diastereoselectivity ^a trans : cis	Enantioselectivity ^b		Yield ^c (%)	[α] _D (c in CHCl ₃) ^d
		trans (% ee)	cis (% ee)		
Styrene	70 : 30	35	6	80	-33.1° (c, 2.5)
α-methylstyrene	62 : 38	-	-	79	-9.7° (c, 3.2)
1-decene	-	-	-	78 ^e	-5.2° (c, 4.2)
2,5-dimethyl-2,4-hexadiene	66 : 34	-	-	60	+2.0° (c, 6.5) ^f

^aDetermined by ¹H-NMR spectrum. ^b% Ee was determined by 400 MHz ¹H NMR spectrum of corresponding methyl esters with Eu(tfc)₃ shift reagent. ^cYield is for mixture of cis and trans compounds. ^dThe specific rotation is for the corresponding acid (mixture of trans and cis). ^eTrans and cis isomers did not separate in ¹H NMR spectrum.

^fThe value is for the trans-cis mixture of corresponding t-butyl esters.

The enantiomeric excess (% ee) of the ethyl and *tert*-butyl cyclopropane carboxylates were determined by the literature procedure.^{19c} The esters were converted to their corresponding acids **33**, **34**, **37**, and **38**. These acids were then treated with diazomethane to get the methyl esters **39** and **40** (Scheme XV). The methyl esters with the shift reagent Eu(tfc)₃ in CDCl₃ showed the separation of peaks for the enantiomers in ¹H NMR spectra. The relative intensities of the peaks gave %ee.



Scheme XV

In all these reactions we observed that on addition of diazoester to Cu(II) complex **30**, a vigorous reaction took place and the colour changed from blue green to red brown. In view of Kochi's inference that cyclopropanation of olefins is mainly catalyzed by Cu(I) which is formed by reduction of Cu(II) with diazomethane, we propose and confirm that, in the present system, Cu(II) is reduced to Cu(I) by diazoesters. The red brown colour of the solution might be due to the colloidal Cu(0) which could be one of the decomposition products of unstable Cu(I) species. This reduction process was confirmed by uv-visible and epr spectroscopy (Figure 3).

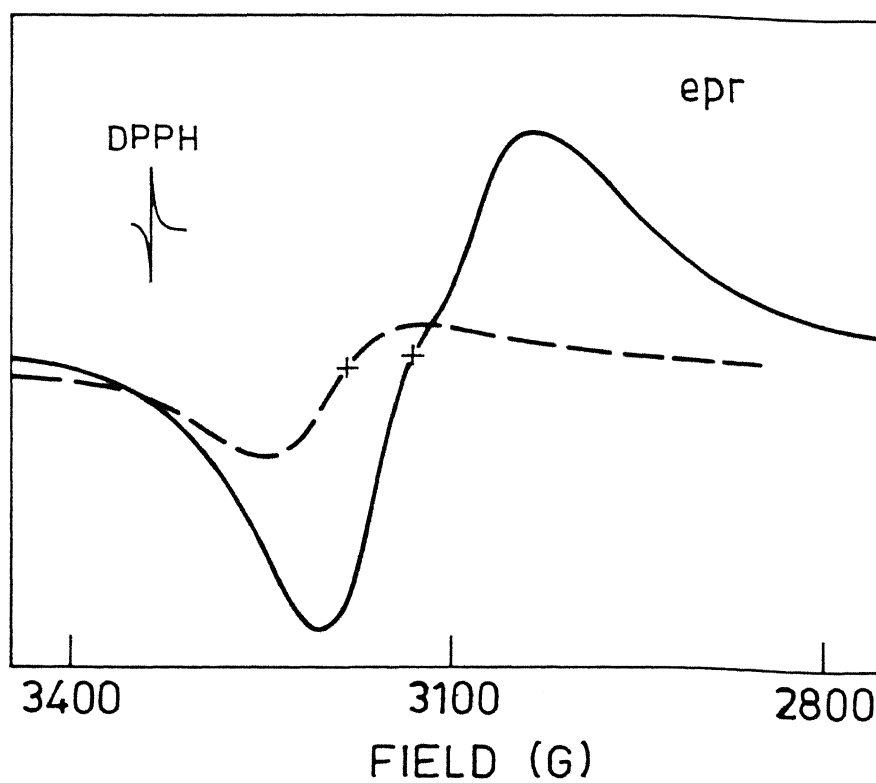
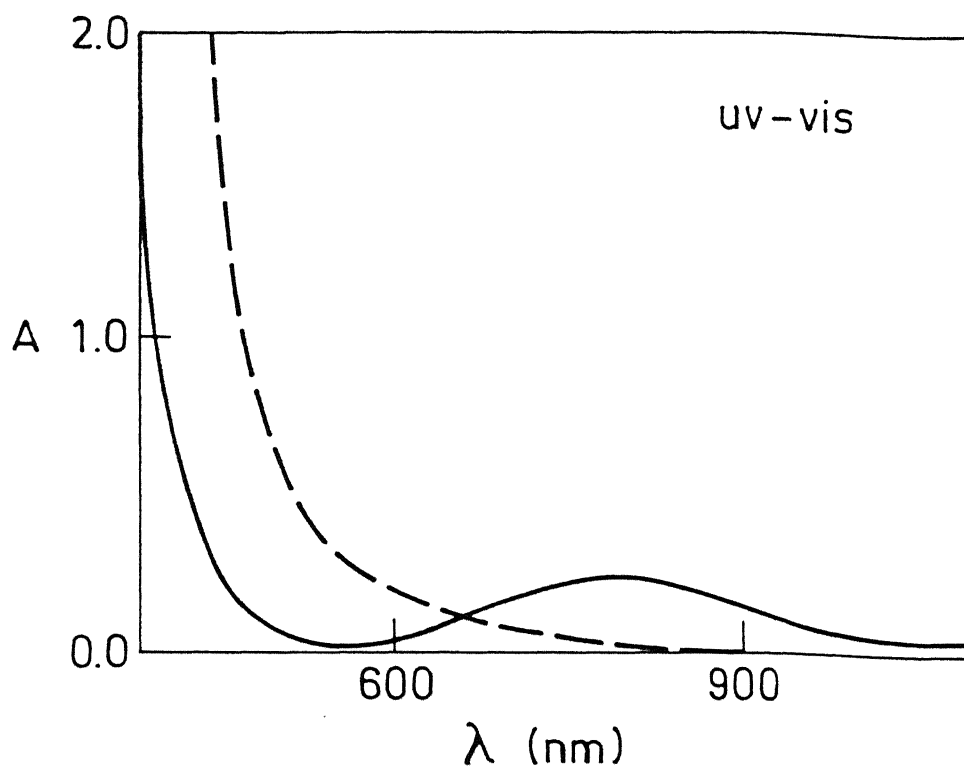


Figure 3: Uv-vis and epr spectra of **30a** (solid line) and after its treatment with ethyldiazoacetate

The Cu(II) complex **30a** shows a d-d transition at λ_{max} 770 nm in uv spectroscopy. It also gives a epr signal ($g=2.133$) which is characteristic of Cu(II) paramagnetic complex. When the solution was treated with ethyl diazoacetate under nitrogen atmosphere, the d-d band disappeared in uv-vis spectrum, and a new signal ($g=2.099$) in epr spectrum was noticed. Since the original epr signal vanished, we thought that the Cu(II) complex was reduced. The new epr signal had one tenth intensity of the original one. This indicated that some Cu(II) complex was still present in the reaction mixture. The difference in g values proved that the nature of new Cu(II) species was different from the original one. This is quite possible due to the instability of Cu(I) species which can disproportionate into Cu(II) and Cu(0). The disproportionation could be due to the absence of favoured geometry for Cu(I).

In the present case, Cu(II) was reduced to Cu(I) using diazoester *in situ* at room temperature. So, the activation of the Cu(II) catalysts with phenyl hydrazine, as shown by Masamune²² & Kanemassa,²⁹ was not needed. Even heating with diazoester, as was done by Pfaltz,¹⁹ was not required.

The facial selectivity in the reaction has been explained using a copper carbenoid structure as depicted in figure 4. The attack of the carbenoid center from it's *Re* face is more favourable due to lesser repulsive interaction built up between the isopropyl and carboxylic ester. If *Si* face of styrene approaches this favourable side of carbenoid center, *trans* (1*R*, 2*R*) enantiomer is obtained as a major product. Analogous approach of this type has been proposed by Pfaltz.^{19c}

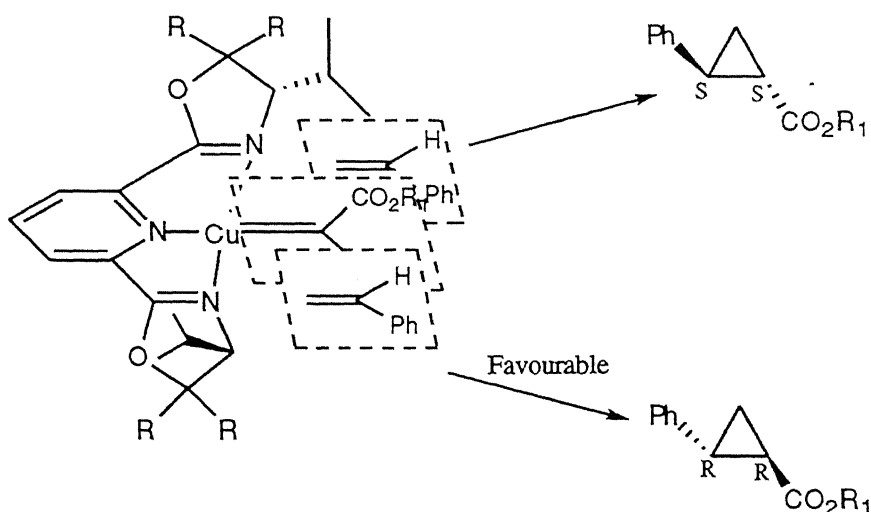
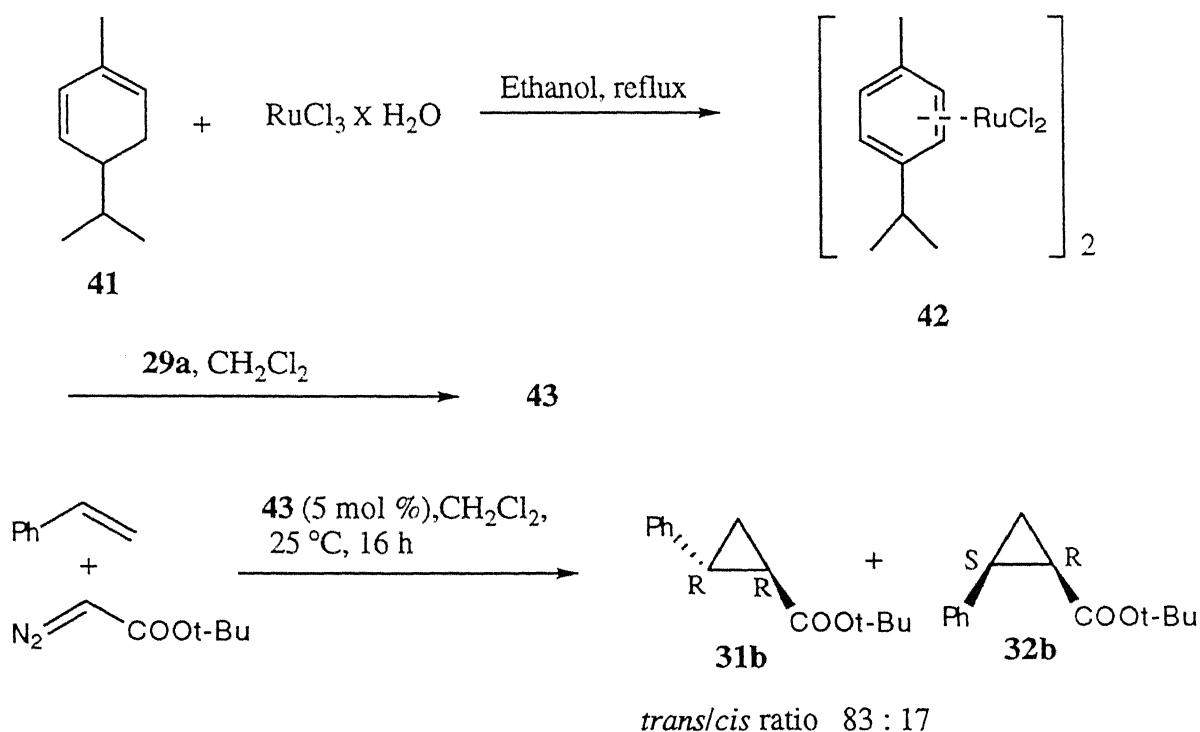


Figure 4

Low enantioselectivity in case of Cu catalyst **30** can only be explained if we consider that the complexation may not be that much rigid as Cu is having small size. So the chiral environment is at a distance from the reaction center. After the aforementioned work was complete,³⁵ a paper appeared in which effect of similar type of ligand complexed with ruthenium chloride was used for cyclopropanation reaction.³⁰ In order to see the effect of Ru metal which is larger in size, we prepared the catalyst **43** by taking **29a** and $[\text{RuCl}_2(\text{p-cymene})]_2$ **42** in CH_2Cl_2 . The **42** was synthesized from α -phellandrene **41**. The complex **43** was used in the cyclopropanation reaction on styrene. The reaction was not that much clean as we got about 24% yield of mixture of fumarate and maleate along with 40% of the cyclopropanated product. Although diastereoselectivity was high (*trans/cis* ratio 83:17), the enantioselectivity was again poor. The *trans*-isomer showed 36% ee and the *cis*-one showed 9% ee.



Scheme XVI

Conclusion

In conclusion, we have synthesized new ligands for enantioselective cyclopropanation reaction of olefins. Although the reaction is not very enantioselective, the diastereoselectivity was high. We have also thrown light on its mechanistic aspects. With the help of uv-visible and epr spectroscopy we have proved that the reaction is catalyzed by Cu(I) and this species is formed *in situ* at room temperature by reduction of Cu(II) complex with a diazoester used in the reaction. Thus, the activation of Cu(II) catalysts by external means is not needed, at least in this case, for this kind of reaction. Change of metal from Cu to Ru for complexation failed to increase the enantioselectivity but the diastereoselectivity was enhanced appreciably.

Experimentals

General Considerations

^1H NMR spectra were recorded on Jeol PMX and Bruker, as mentioned in the experimentals, using TMS as internal standard. Chemical shifts are reported in δ , ppm, and coupling constants in Hz. IR spectra were recorded on Perkin-Elmer 580 and 1320 spectrometers using samples as either neat liquid or as KBr disc. Optical rotations were taken on Rudolph Autopol-II automatic polarimeter. X-band EPR spectra were recorded in chloroform at 298K on a Varian E-109C spectrometer and calibrated with the help of DPPH ($g=2.0023$). UV-visible spectra were recorded in chloroform or Shimadzu UV-160. Elemental (C, H, N) analyses were done on Perkin-Elmer 240-C automatic elemental analyzer. Mass spectrometric analyses were done on Jeol D-300 (EI/CI) and Jeol SX-102 (FAB) instruments.

Pyridine-2,6-dicarbonyl chloride or dipicolinyl chloride **26** was prepared by the standard procedure as given by Cram *et. al.*³⁷ (*S*)-(-)-2-Amino-3-methyl-1,1-diphenyl butane-1-ol **27a** and (*S*)-(-)-2-amino-3-methyl-1,1-diethyl butane-1-ol **27b** were made following the literature procedure.³⁸ Ethyl diazoacetate,⁴⁰ *tert*-butyl diazoacetate⁴¹ and diazomethane⁴³ were synthesized using the known procedures. $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ was prepared by the literature method.⁴² Tris[3-(trifluoromethyl hydroxy methylene)d-camphorato]europium(III), i.e., $\text{Eu}(\text{tfc})_3$, was purchased from Fluka. Dipicolinic acid, (*S*)-valine, CaH_2 , Mg turnings, toluene-4-sulfonyl chloride, *tert*-butyl acetoacetate, styrene, α -methyl styrene, 1-decene, 2,5-dimethyl-2,4-hexadiene were Fluka compounds. Methanesulfonic acid was obtained from E-Merck. $\text{RuCl}_3 \times \text{H}_2\text{O}$, sodium azide, sodium nitrite and triethylamine were purchased from S.D.Fine Chem. Ltd. $\text{Cu}(\text{OTf})_2$ and trifluoroacetic acid were Aldrich chemicals.

All the reactions were carried out using freshly distilled and dry solvents from solvent stills. Reagent grade solvents were obtained from Nice or S.D.Fine Chem. Ltd. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane, chloroform, dichloroethane and triethylamine were distilled over CaH_2 . Methanol and ethanol were dried by refluxing and distilling over Mg turnings. Routine monitoring of reactions was performed using tlc grade silica gel-G from Acme. Organic extracts were dried over *anhydrous* sodium sulfate (purchased from S.D. Fine Chem. Ltd.) and concentrated *in vacuo*. Evaporation of solvents was

performed at reduced pressure, using a Büchi rotary evaporator. All the chromatographic separations were done by using silica gel (Acme's 60-120 mesh). Petroleum ether (60 - 80° range) and ethylacetate were used as solvents for chromatography.

Preparation of pyridine-2,6-dicarbonyl chloride 26: A mixture of dipicolinic acid (500 mg, 2.99 mmol) and excess of SOCl_2 (3.27 mL, 44.87 mmol) was refluxed for 10 h. Most of the SOCl_2 was distilled off. Its complete removal was affected by using vacuum pump (with KOH trap). On cooling, we got **26** as a solid product; mp 58 °C (lit. mp 56 °C)³⁷.

General Procedure for the Preparation of Aminoalcohols³⁸ 27: The (*S*)-valine (1.17 g, 10 mmol) was added in portions to a stirred solution of SOCl_2 (800 μL , 11 mmol) in methanol (3 mL) at 0 °C. The mixture was slowly warmed to 40 °C and further stirred for 2 h. Most of the methanol was removed on rotary evaporator. Drying of the residue under vacuum at 100 °C for 1 h gave aminoester hydrochloride salt (1.50 g, 9 mmol) as a solid which was added, in portions, to a preformed Grignard reagent [prepared from Mg turnings (1.94 g, 80 mmol) and corresponding bromide (71 mmol)] in THF (25 mL) at 0 °C. The reaction mixture was stirred for 7 h (0 °C to rt). The crude mixture was slowly decomposed by cold, saturated aqueous NH_4Cl solution. The organic layer was separated and kept aside. The aqueous layer was saturated with NaCl and extracted (three times) with ethylacetate. The organic layers were combined and dried. The solvent was evaporated to get the crude product.

(*S*)-(-)-2-Amino-3-methyl-1,1-diphenylbutane-1-ol 27a: The crude product was purified by filtration through silica-gel column followed by crystallization from 10:1 (v/v) mixture of EtOH and water; Yield 40% as a white solid; mp 90 °C; R_f 0.50 (1:4 EtOAc in petroleum ether); $[\alpha]_D^{25} -127^\circ$ (*c* 1.5, CHCl_3); IR (KBr) 3400, 3340, 3080, 2970, 1585, 1485, 1440, 1170 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.90 (d, *J* = 7 Hz, 6H), 1.10 - 2.10 (m, 3H), 3.76 (d, *J* = 2Hz, 1H), 6.90 - 7.80 (aromatics, 10H).

(*S*)-(-)-2-Amino-3-methyl-1,1-diethylbutane-1-ol 27b: The crude product shows pure compound. Yield 47% as a gummy solid; R_f 0.26 (100% EtOAc); $[\alpha]_D^{25} -20.3^\circ$ (*c* 1.5, CHCl_3); IR (neat) 3400, 3345, 2960, 1170 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.50 - 1.10 (m, 12H), 1.10 - 1.60 (m, 5H), 1.90 (broad singlet, 3H), 2.4 (d, *J* = 2Hz, 1H).

General Procedure for Synthesis of Amides 28: A solution of aminoalcohol **27** (3.0 mmol) and triethylamine (7.6 mmol) in anhydrous CH_2Cl_2 (10 ml) was added dropwise to dipicolinyl chloride **26** (1.5 mmol) at 0 °C. The reaction mixture was stirred for 16 h (0 °C - rt). It was diluted with dichloromethane and washed with aq. NaHCO_3 , water, brine and dried. Solvent removal gave solid mass which, after washing with petroleum ether was chromatographed over silica gel to give product as a solid mass.

N,N'-bis[1'-(S)-isopropyl-2',2'-diphenyl-2'-hydroxyethyl]-2,6-pyridine

dicarboxamide 28a: Yield 90% as a solid mass; mp 110 °C; R_f 0.22 (1:4, EtOAc in petroleum ether); $[\alpha]_D^{25}$ -46.2° (c 1.0, CHCl_3); IR (KBr) 3400, 3060, 1650 cm^{-1} ; ^1H NMR (CDCl_3 , 80 MHz) δ 0.95 (d, J = 6.5 Hz, 12H), 1.95 (m, 2H), 3.00 (bs, 2H, -OH), 5.12 (dd, J = 10, 2.5 Hz, 2H), 6.90 - 8.50 (m, 23H & -NH). Anal. calcd for $\text{C}_{41}\text{H}_{43}\text{N}_3\text{O}_4$: C, 76.76; H, 6.71, N, 6.55; Found: C, 76.12; H, 6.86; N, 6.70.

N,N'-bis[1'-(S)-isopropyl-2',2'-diethyl-2'-hydroxyethyl]-2,6-pyridine

dicarboxamide 28b: Yield 85% as a solid mass; R_f 0.50 (2:3, EtOAc in petroleum ether); $[\alpha]_D^{25}$ -3.6° (c 0.6, CHCl_3); IR (KBr) 3500, 3400, 1660 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.65 - 1.25 (m, 24H), 1.25 - 1.80 (m, 10H), 2.5 (bs, 2H, -OH), 4.00 (dd, J = 10, 2.5 Hz, 2H), 8.3 (aromatics, 3H). Anal. calcd for $\text{C}_{25}\text{H}_{43}\text{N}_3\text{O}_4$: C, 66.82; H, 9.58, N, 9.35; Found: C, 66.06; H, 9.83; N, 9.50.

General Procedure for Cyclization³⁹ to 29: A solution of aminoalcohol (1.1 mmol) in CH_2Cl_2 (15 mL) was refluxed with methanesulfonic acid (425 μl , 6.6 mmol) for 6 h while keeping CaH_2 in an addition funnel for removing the water generated during the reaction. The reaction mixture was cooled down and 15 mL of CH_2Cl_2 was added. It was washed with aq. NaHCO_3 , water, brine and dried. Solvent removal gave solid mass which was chromatographed over silica gel to afford pure compound.

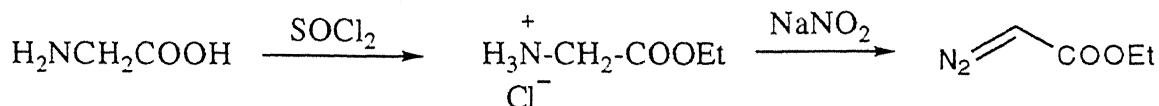
2,6-Bis[5',5'-diphenyl-4'-(S)-isopropyl oxazolin-2'-yl]pyridine 29a: The cyclized product **29a** was obtained as solid in 85% yield; mp 65 - 66 °C; R_f 0.55 (1:4, EtOAc:petroleum ether); $[\alpha]_D^{25}$ -233.2° (c 2.7, CHCl_3); IR (KBr) 3060, 1650 cm^{-1} ; ^1H NMR (CDCl_3 , 80 MHz) δ 0.68 (d, J = 6 Hz, 6H), 1.09 (d, J = 6 Hz, 6H), 1.95 (m, 2H), 4.93 (d, J = 5 Hz, 2H), 6.9 - 8.5 (aromatics, 23H); ^{13}C NMR (CHCl_3 , 75.469 Hz) δ 17.10, 21.77, 30.10, 80.10, 93.50, 125.27,

126.07, 126.73, 127.18, 127.56, 127.71, 128.15, 137.58, 140.13, 144.78, 146.62, 160.11; MS (Fab, m/z): 606 (M^++1), 297, 167. Anal. calcd for $C_{41}H_{39}N_3O_2$: C, 81.32; H, 6.45, N, 6.94; Found: C, 80.71; H, 6.52; N, 7.02.

2,6-Bis[5',5'-diethyl-4'-(S)-isopropyl oxazolin-2'-yl]pyridine 29b: 80% yield as sticky solid; R_f 0.58 (2:3, EtOAc:petroleum ether); $[\alpha]^{25}_D$ -37.1° (c 1.4, $CHCl_3$); IR (film) 1650 cm^{-1} ; 1H NMR (CCl_4 , 60 MHz) δ 0.6-1.4 (m, 24H), 1.8 (m, 10H), 3.6 (d, $J = 7$ Hz, 2H), 8.0 (aromatics, 3H); MS (Fab, m/z): 437 ($M^++Na + 1$), 436 (M^++Na , base peak), 125, 69. Anal. calcd for $C_{25}H_{39}N_3O_2$: C, 72.64; H, 9.44, N, 10.17; Found: C, 72.12; H, 9.52; N, 10.28.

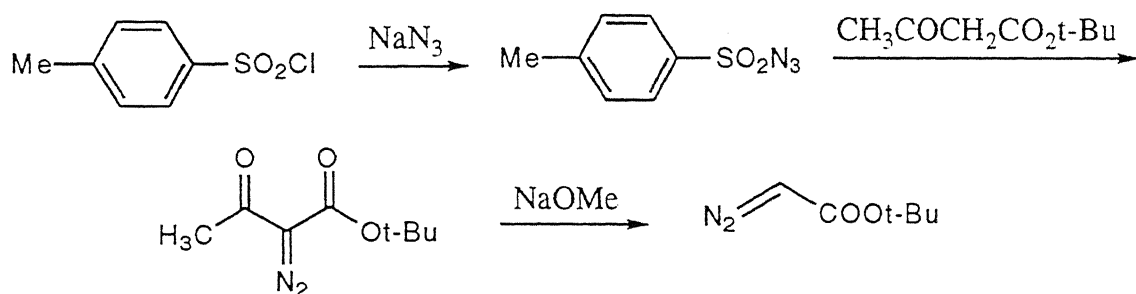
Preparation of Cu(II) complex of 29a: Ligand **29a** (0.082 mmol) and stoichiometric amount of $Cu(OTf)_2$ were taken in dry $CHCl_3$ (2 mL). The whole reaction mixture was stirred at r.t. for 1 h and the solvent was evaporated to get a blue green solid in quantitative yield; mp 164 °C; MS (Fab, m/z): 668 (Ligand-Cu, base peak).

Preparation of Ethyl diazoacetate⁴⁰:



Glycine (10 g, 133.2mmol) was added, in portions, to a stirred solution of $SOCl_2$ (17.44 g, 146.5 mmol) in ethanol (3 mL) at 0 °C. The mixture was slowly warmed to 40 °C and further stirred for 2 h. Most of the ethanol was removed on rotary evaporator. Drying of the residue under vacuum at 80 °C for 1 h gave aminoester hydrochloride salt as a solid (15 g, 81% yield). A solution of this hydrochloride salt (108.2 mmol) in water (30 mL) was mixed with CH_2Cl_2 (65 mL) under N_2 . The solution was cooled to -5 °C and an ice cold solution of $NaNO_2$ (8.96 g, 129.89 mmol) in 25 mL water was added with stirring. The temperature was lowered to -20 °C and 10.2 g of 5% H_2SO_4 (w/w) was added dropwise for couple of minutes. After 10 min of further stirring, organic layer was separated. Aqueous layer was extracted with CH_2Cl_2 . Combined organic extracts were washed twice with cold 5% $NaHCO_3$ and dried. CH_2Cl_2 was removed using aspirator by keeping the bath temperature around 30 °C to get the product; Yield 50%; 1H NMR (CCl_4 , 60 MHz) δ 1.30 (t, $J = 7$ Hz, 3H), 4.16 (q, $J = 7$ Hz, 2H), 4.70 (s, 1H).

Preparation of *tert*-Butyl diazoacetate⁴¹:



A solution of NaN_3 (2 g, 30.76 mmol) in water (5 mL) and EtOH (10 mL) was treated with a warm ($\sim 45^\circ\text{C}$) solution of *p*-toluenesulfonyl chloride (5.33 g, 28 mmol) in EtOH (30 mL) with stirring. The reaction mixture was stirred at room temperature for 2.5 h. Most of the solvent was removed at 35°C using a rotary evaporator (40 mm). The residue was mixed with 30 mL of water in a separatory funnel and the oil was separated. It was washed with water, dried, and filtered with suction to get oily *p*-toluenesulfonyl azide (4 g, 72% yield). ^1H NMR (CCl_4 , 60 MHz) δ 2.50 (s, 3H), 7.60 (aromatics, 4H).

To a mixture of *t*-butyl acetoacetate (3.21 g, 20.28 mmol) in dry CH_3CN (25 mL) and Et_3N (2.052 mL, 20.28 mmol), *p*-toluenesulfonyl azide (4 g, 20.28 mmol) was added dropwise with vigorous stirring over 10-15 min. The addition caused little warming of the reaction mixture which turned yellow. It was stirred for 2.5 h at room temperature. The solvent was evaporated at 35°C . The residue was mixed with 30 mL ether and washed with 1.2 g KOH in 15 mL water, 0.21 g KOH in 10 mL water and 10 mL water successively. Organic layer was dried and the solvent was evaporated at 35°C to get 3.6 g of *t*-butyl α -diazoacetoacetate; Yield 99%; ^1H NMR (CCl_4 , 60 MHz) δ 1.50 (s, 9H), 2.36 (m, 3H).

The *t*-butyl α -diazoacetoacetate (3.6 g, 19.54 mmol) was taken in 6 mL MeOH. This solution was cooled to $2-3^\circ\text{C}$ in an ice bath and a solution of NaOMe (prepared from 450 mg Na and 6 mL MeOH) was added to it with stirring over a period of 30 min. After the addition was complete, the mixture was stirred in the ice bath for another 30 min. The red reaction mixture was taken in 40 mL ice water and was extracted with 20 mL of ether. The aqueous phase was saturated with NaCl and extracted with two 20 mL portions of ether. The combined ethereal extracts were washed with 20 mL water and dried. Ether was removed using rotary evaporator at 30°C and the

crude was distilled under vacuum to get the pure *t*-butyl diazoacetate; Yield 50%; bp 55 °C (9 mm) [lit. bp 51 - 53 °C]⁴¹; ¹H NMR (CCl₄, 60 MHz) δ 1.46 (s, 9H), 4.50 (s, 1H).

General Procedure for Cyclopropanation Reaction of olefins and diazoacetate using the catalyst 30: The ligand **29** (0.08 mmol) and Cu(OTf)₂ (0.08 mmol) were taken in 3 mL CHCl₃ and stirred at rt for 1 h to generate the catalyst **30** *in situ*. The blue-green coloured reaction mixture was filtered. The filtrate was added to the olefin (32 mmol) solution in the chosen solvent (3 mL) at room temperature. Then, diazoester (7.9 mmol) solution in 3 mL of the same solvent was added at the rt over a period of 4 h. It was stirred for 16 h. The solvent was removed and the crude was chromatographed over silicagel to give cyclopropyl esters in 60 - 95% yield.

Cyclopropanation of styrene with ethyl diazoacetate using the catalyst 30a: The cyclopropanation reaction was carried out in CHCl₃ following the above general procedure; Yield 93% as a viscous liquid; *R_f* 0.72 and 0.66 (1:9, EtOAc in petroleum ether) for a mixture of *trans*- and *cis*-compounds, **31a** and **32a**; [α]_D²⁵ -26.1° (*c* 9.5, CHCl₃); IR (neat) 2980, 1710, 1595, 1490, 1450, 1400, 1170, 1040 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 0.99 (t, *J* = 7 Hz, *cis*-isomer), 1.25 (t, *J* = 7 Hz, *trans*-isomer), 1.25 - 2.10 (m, 3H), 2.10 - 2.70 (m, 1H); 3.80 (q, *J* = 7 Hz, *cis*-isomer), 4.10 (q, *J* = 7 Hz, *trans*-isomer), 6.90 - 7.40 (aromatics, 5H).

Ratio of *trans*- and *cis*-isomers was found to be 66:34 from ¹H NMR. This was further confirmed by conversion to their methyl esters. The *trans*-isomer shows 28% ee and the *cis*-isomer 8% ee.

Similarly the catalyst **30b** gave the cyclopropanated products, **31a** and **32a**, in 86% yield (*trans*/*cis* ratio: 64:36). The enantioselectivity was 26% for the *trans*-compound. The *cis*-isomer did not show any enantioselectivity in this case (Table 1).

Cyclopropanation of styrene with *tert*-butyl diazoacetate using the catalyst 30a: The cyclopropanation reaction was carried out in CHCl₃ following the above general procedure; Yield 80% as a viscous liquid; *R_f* 0.78 and 0.70 (1:9 EtOAc in petroleum ether) for a mixture of *trans*- and *cis*-isomers, **31b** and **32b**; [α]_D²⁵ -30.5° (*c* 8.0, CHCl₃); IR (neat) 2980, 1715, 1600, 1450, 1390, 1365, 1150 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 0.80 - 2.60 (m, 4H), 1.10 (s, -C(CH₃)₃ for *cis*-isomer), 1.40 (s, -C(CH₃)₃ for *trans*-isomer), 6.90 - 7.40 (aromatics, 5H).

Ratio of *trans*- and *cis*-isomers was found to be 70:30 from ^1H NMR. The *trans*-isomer shows 35% ee and the *cis*-isomer 6% ee.

Similarly the catalyst **30b** gave the cyclopropanated products, **31b** and **32b**, in 95% yield (*trans/cis* ratio: 70:30). The enantioselectivity, in case of *trans*-compound, was 33% (Table 1).

Cyclopropanation of α -methyl styrene with *tert*-butyl diazoacetate using the catalyst 30a: The reaction was performed in CHCl_3 as per the general procedure; Yield 79% as viscous liquid; R_f 0.78 and 0.61 (1:20, EtOAc in petroleum ether); $[\alpha]^{25}_{\text{D}} -8.5^\circ$ (c 4, CHCl_3); IR (neat) 2970, 1710, 1590, 1440, 1380 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.60 - 2.60 (m, 3H), 1.10 (s, $-\text{C}(\text{CH}_3)_3$ for *cis*-isomer), 1.40 (s, $-\text{C}(\text{CH}_3)_3$ for *trans*-isomer and CH_3 protons), 6.93 - 7.43 (aromatics, 5H).

Ratio of *trans* - and *cis* -isomers, **35b** and **36b**, was found to be 62:38 from ^1H NMR. This was further confirmed by conversion to their methyl esters (Table-3).

Cyclopropanation of 1-decene with *tert*-butyl diazoacetate using the catalyst 30a: The reaction was done in CHCl_3 ; Yield 78% as a viscous liquid; R_f 0.64 and 0.51 (1:20, EtOAc in petroleum ether); $[\alpha]^{25}_{\text{D}} -5.0^\circ$ (c 3.5, CHCl_3); IR (neat) 2930, 2860, 1715, 1360, 1100 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.66 - 2.0 (m, 4H); 0.90 (m, 3H); 1.36, 1.43 (two singlets, 23H).

Cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *tert*-butyl diazoacetate using the catalyst 30a: The reaction was done in CHCl_3 ; Yield 60%; R_f 0.81 and 0.64 (1:20, EtOAc in petroleum ether); $[\alpha]^{25}_{\text{D}} +2.0^\circ$ (c 6.5, CHCl_3); IR (neat) 2870, 2820, 1710, 1360, 1305, 1140 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.10 - 1.30 (m, 6H), 1.50 (d, $J = 4$ Hz, 12 H), 1.70 (split singlet, 5H), 4.93 (dd, $J = 8$ Hz, 2 Hz, *trans* -isomer), 5.40 (dd, $J = 8$ Hz, 2 Hz, *cis* -isomer), 6.06 (s, $\text{CH}=\text{CH}$ for maleate), 6.70 (s, $\text{CH}=\text{CH}$ for fumarate).

The sample contained some amount of fumarate and maleate. Ratio of *trans*- and *cis*-isomers was found to be 66:34 from ^1H NMR.

Preparation of $[\text{RuCl}_2(\text{p-cymene})]_2$ **42:** The crude $\text{RuCl}_3 \times \text{H}_2\text{O}$ was heated (hot plate) with concentrated HCl to dryness for several times. Finally, it was dried under reduced pressure. The final residue was dissolved in EtOH and then filtered to remove any insoluble material. The filtrate contained the desired pure $\text{RuCl}_3 \times \text{H}_2\text{O}$ in solution. A slight excess of α -phellandrene **41**

was added to the above filtrate and the mixture was heated to reflux for about 4 h. The colour initially changed from red to blue green, and then, finally to orange red. The solvent was removed and the solid residue was dissolved in CH_2Cl_2 and filtered through neutral alumina by eluting with CH_2Cl_2 . It was concentrated and petroleum ether was added to induce precipitation. Finally, the complex was separated by centrifugation and washed several times with petroleum ether. The orange brown solid was dried in vacuum over phosphorous pentoxide at refluxing ethanol temperature. ^1H NMR (CCl_4 , 60 MHz) δ 1.26 (d, $J = 7$ Hz, 6H), 2.16 (s, 3H), 2.60 - 3.10 (m, 1H), 5.36 (q $J = 6$ Hz, 4H).

Cyclopropanation of styrene with *tert*-butyl diazoacetate using the catalyst 43: The ligand **29a** (21 mg, 0.035 mmol) and **42** were taken in dry CH_2Cl_2 (1 mL). Styrene (1 mL, 8.8 mmol) was added to the reaction mixture and stirred for 2 h at room temperature. Then, *tert*-butyl diazoacetate (250 mg, 1.760 mmol) in CH_2Cl_2 (2 mL) was added with the help of motor syringe pump over a period of 8 h. The whole reaction mixture was stirred for another 6 h. Solvent was removed and it was filtered through a column to get a viscous liquid; Yield 40% (24% of fumarate and maleate was also formed); ^1H NMR (CCl_4 , 60 MHz) δ 0.80 - 2.60 (m, 4H), 1.10 (s, $-\text{C}(\text{CH}_3)_3$), 1.40 (s, $-\text{C}(\text{CH}_3)_3$), 6.06 (s, $\text{CH}=\text{CH}$, maleate), 6.70 (s, $\text{CH}=\text{CH}$, fumarate), 6.90 - 7.40 (aromatics, 5H).

Ratio of *trans*- and *cis*-isomers, **31b** and **32b** was found to be 83:17 from ^1H NMR. The *trans*-isomer shows 36% ee and the *cis*-isomer 9% ee (Scheme XVI).

Determination of Diastereoselectivity and Enantiomeric Excess: The ethyl and *tert*-butyl cyclopropyl esters were converted to corresponding acids **33**, **34**, **37** and **38** which were then treated with diazomethane to get the methyl esters **39** and **40** (Scheme-XV). The methyl esters and shift reagent, $\text{Eu}(\text{tfc})_3$ were taken in CDCl_3 and 400 MHz ^1H NMR spectrum was run. Both the diastereoselectivity and enantioselectivity were determined from the ^1H NMR spectrum of each sample following the literature procedure.¹⁹

Hydrolysis of ethyl-2-phenyl cyclopropane-1-carboxylate: The mixture of ethyl esters, **31a** and **32a**, (500 mg, 2.63 mmol) was refluxed for 4 h with MeOH (9.5 mL) and 25% aqueous NaOH (5.8 mL). It was brought to room temperature and MeOH was removed. The mixture was diluted with water and extracted with ether twice. The organic layer was washed with brine and

dried. It was concentrated to get yellow oil as product; Yield 60-75%; IR (neat) 3000-2500 (broad peak), 1780, 1440, 1230, 930, 745, 690 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.09 - 2.10 (m, 3H), 2.15 - 2.85 (m, 1H), 6.90 - 7.30 (m, 5H), 9.66 (s, 1H, COOH).

General Procedure for the hydrolysis of *tert*-butyl-2-substituted cyclopropane-1-carboxylate: The mixture of *trans*- and *cis*-isomers of *tert*-butyl esters, **31b** and **32b**, (0.46 mmol) was dissolved in CF_3COOH (2 mL) and stirred at room temperature for 10 min. Excess CF_3COOH was removed under vacuum. The residue was taken up in benzene and evaporated. This operation was done thrice to ensure complete removal of moisture. The crude product was dissolved in CH_2Cl_2 , filtered and concentrated to get the acids, **37** and **38** (Filtration removes fumaric acid and maleic acid formed from corresponding esters).

Preparation of the acid derivatives, 37a and 38a, of *tert*-butyl-2-phenyl cyclopropane-1-carboxylate: Reaction was performed as per the general procedure. Yield was almost quantitative. IR (neat) 3000-2500 (broad peak), 1780, 1440, 1230, 930, 690 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.09 - 2.10 (m, 3H), 2.15 - 2.85 (m, 1H), 6.90 - 7.30 (m, 5H), 9.66 (s, 1H, COOH).

Preparation of the acid derivatives, 37b and 38b, of *tert*-butyl-2-methyl-2-phenyl cyclopropane-1-carboxylate: This was performed as per the general procedure. Yield 85%; $[\alpha]^{25}_{\text{D}} -9.68^\circ$ (*c* 3.2, CHCl_3); IR (neat) 3100-2500 (broad peak), 1685, 1485, 1435 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.96 - 2.30 (m, 3H); 1.50 (d, *J* = 5 Hz, 3H); 7.15 (aromatics, 5H); 12.0 (s, 1H, COOH).

Preparation of the acid derivatives, 37c and 38c, of *tert*-butyl-2-octyl cyclopropane-1-carboxylate: The reaction was performed as per the general procedure. Yield 98%; $[\alpha]^{25}_{\text{D}} -5.23^\circ$ (*c* 4.2, CHCl_3); IR (neat) 3100-2500 (broad peak), 1685, 1450, 1425, 1225 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.60 - 2.0 (m, 7H), 1.30 (broad singlet, 14H).

General procedure for the preparation of methylester of cyclopropane carboxylic acid: Diazomethane in ether was prepared according to the literature procedure⁴³ from *N*-nitrosomethyl urea⁴⁴. The mixture of *trans*- and *cis*-carboxylic acids, **37** and **38**, was dissolved in CH_2Cl_2 : ether (1:1) solution. Then diazomethane in ether was added dropwise at 0 $^\circ\text{C}$ with continuous shaking. Addition was continued till the yellow colour persists indicating the presence

of excess diazomethane in the reaction mixture. Solvent was removed and the crude was filtered through a small pad of silica gel to get the mixture of *trans* and *cis*-methyl cyclopropane-1-carboxylates, **39** and **40**.

Preparation of *trans* and *cis* -methyl-2-phenyl cyclopropane-1-carboxylates, 39a and 40a: This was prepared according to the general procedure. Yield 87-90%; ^1H NMR (CDCl_3 , 400 MHz) δ 1.22 - 1.36 (m), 1.56 - 1.68 (m), 1.87 - 1.95 (m, *trans* -isomer), 2.05 - 2.20 (m, *cis* -isomer), 2.56 - 2.64 (m), 3.44 (s, CH_3 , *cis* isomer), 3.73 (s, CH_3 , *trans* isomer), 7.07 - 7.34 (m, aromatics, 5H).

The ratio of the two peaks at δ 3.44 ppm for *cis* -isomer **39a** and at δ 3.73 ppm for *trans* -isomer **40a** gave the diastereoselectivity.

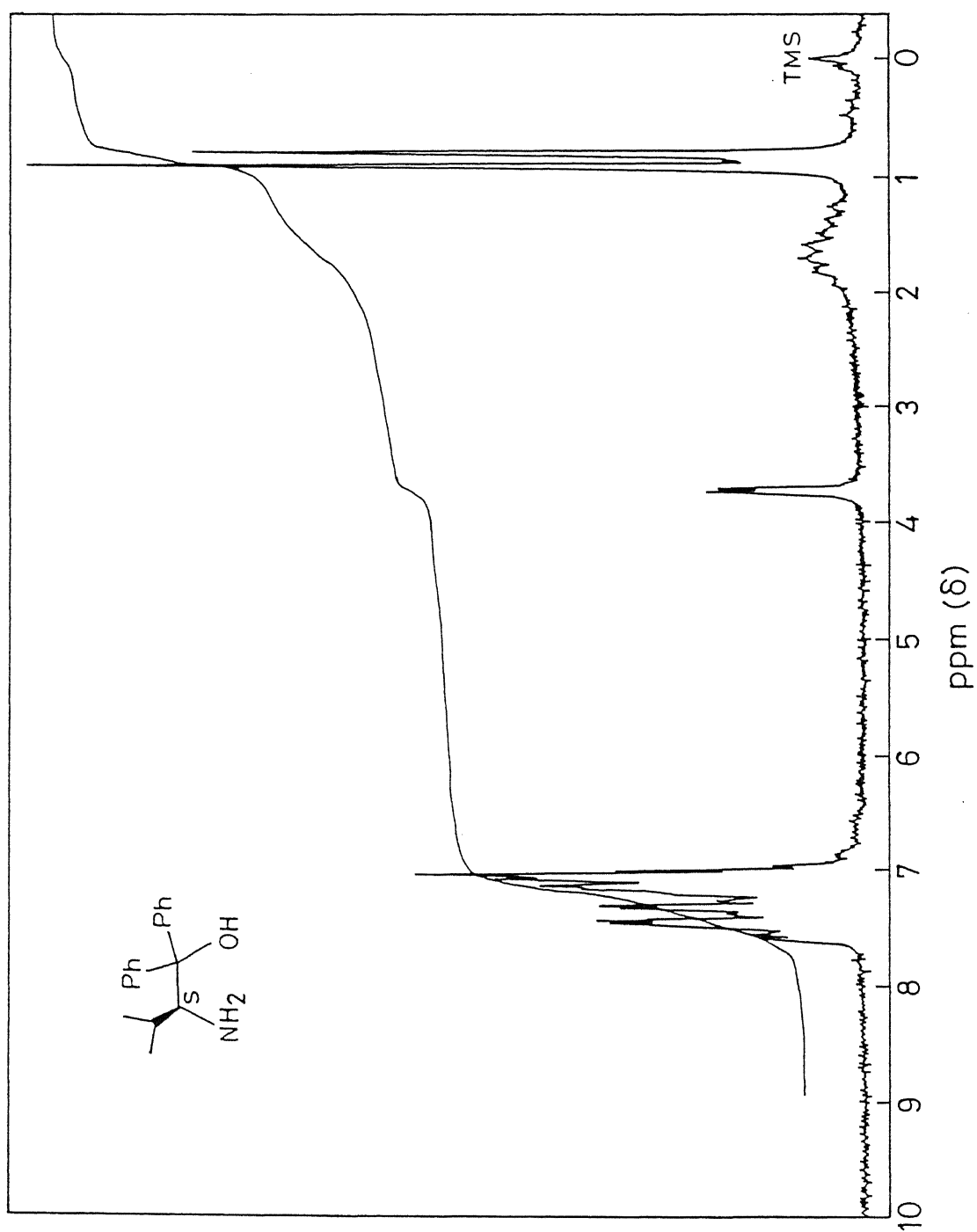
Enantioselectivity was determined, using the shift reagent, $\text{Eu}(\text{tfc})_3$. The methyl esters and shift reagent were taken in CDCl_3 and 400 MHz spectrum was run. The original methyl ester singlet at δ 3.44 for *cis*-diastereomer **39a** got separated into two peaks, δ 3.51 (major) and δ 3.53 (minor). Likewise, the singlet at δ 3.73 *trans*-isomer **40a** got separated into two peaks, δ 3.92 (major) and δ 3.943 (minor). Considering the relative intensities of the peaks, the enantiomeric excess was determined and the results are given in Tables 1, 2, 3 and in Scheme-XVI.

Preparation of *trans* and *cis*-methyl-2-methyl-2-phenyl cyclopropane-1-carboxylates, 39b and 40b: This was prepared according to the general procedure. Yield 94%; R_f 0.75 and 0.65 (1:9 EtOAc in petroleum ether); ^1H NMR (CDCl_3 , 400 MHz) δ 1.18 (m), 1.26 (s), 1.46 (m), 1.54 (m), 1.57 (s), 1.78 (t, $J = 6$ Hz), 1.96 (m), 3.36 (s, CH_3 , *cis* -isomer), 3.75 (s, CH_3 , *trans* -isomer), 7.17 - 7.38 (aromatics, 5H).

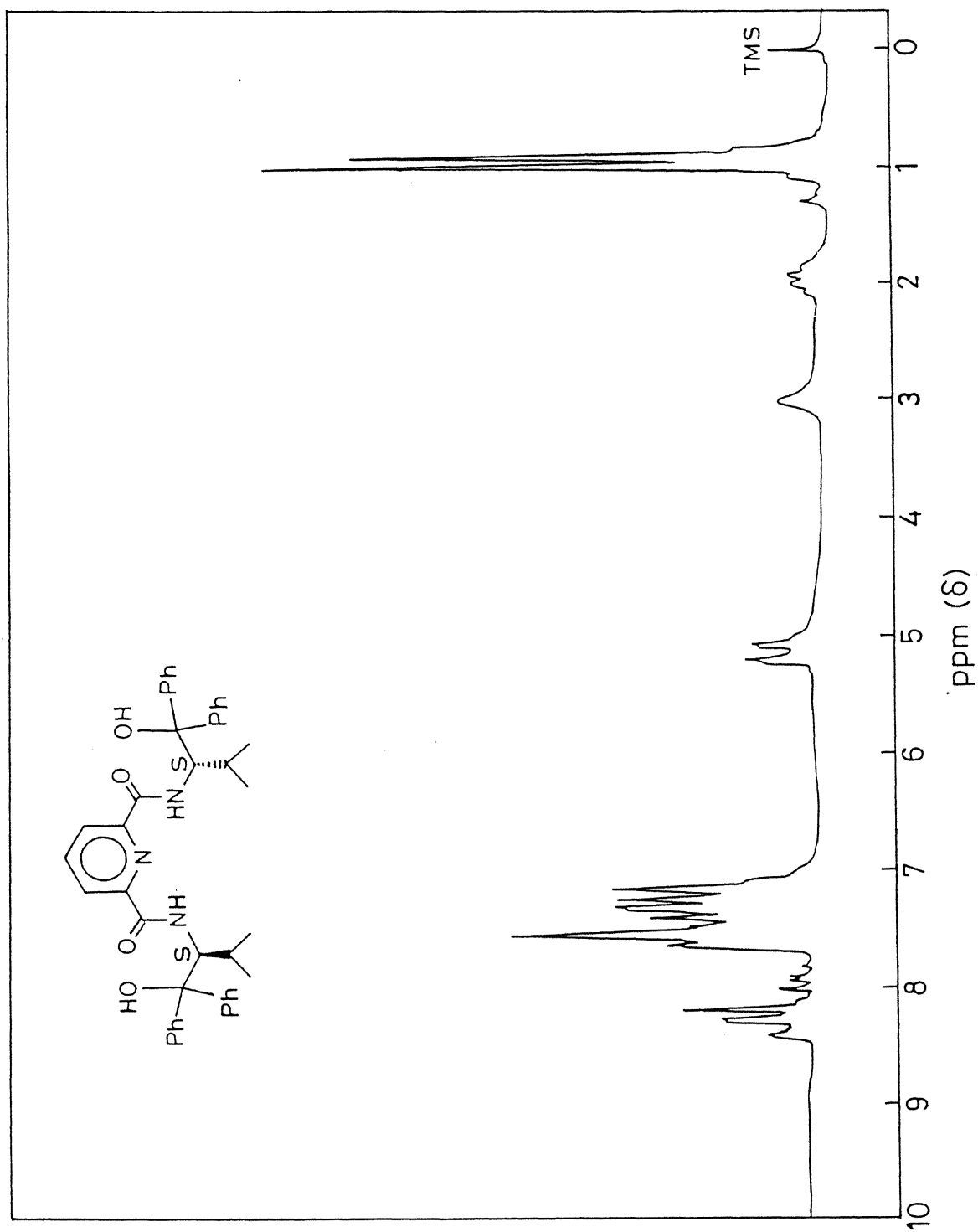
Ratio of the *trans* -and *cis* -isomers, **39b** and **40b**, was found to be 62:38. With the addition of the shift reagent, the original peaks were shifted but the enantiomers were not separated in the ^1H NMR spectrum.

Preparation of *trans* and *cis* -methyl-2-octyl cyclopropane-1-carboxylates, 39c and 40c: This was prepared as per the general procedure. Yield 95%; R_f 0.77 and 0.69 (1:9 EtOAc in petroleum ether); ^1H NMR (CCl_4 , 60 MHz) δ 0.90 (m, 3H), 1.30 (m, 18 H), 3.63 (s, CH_3 , 3H).

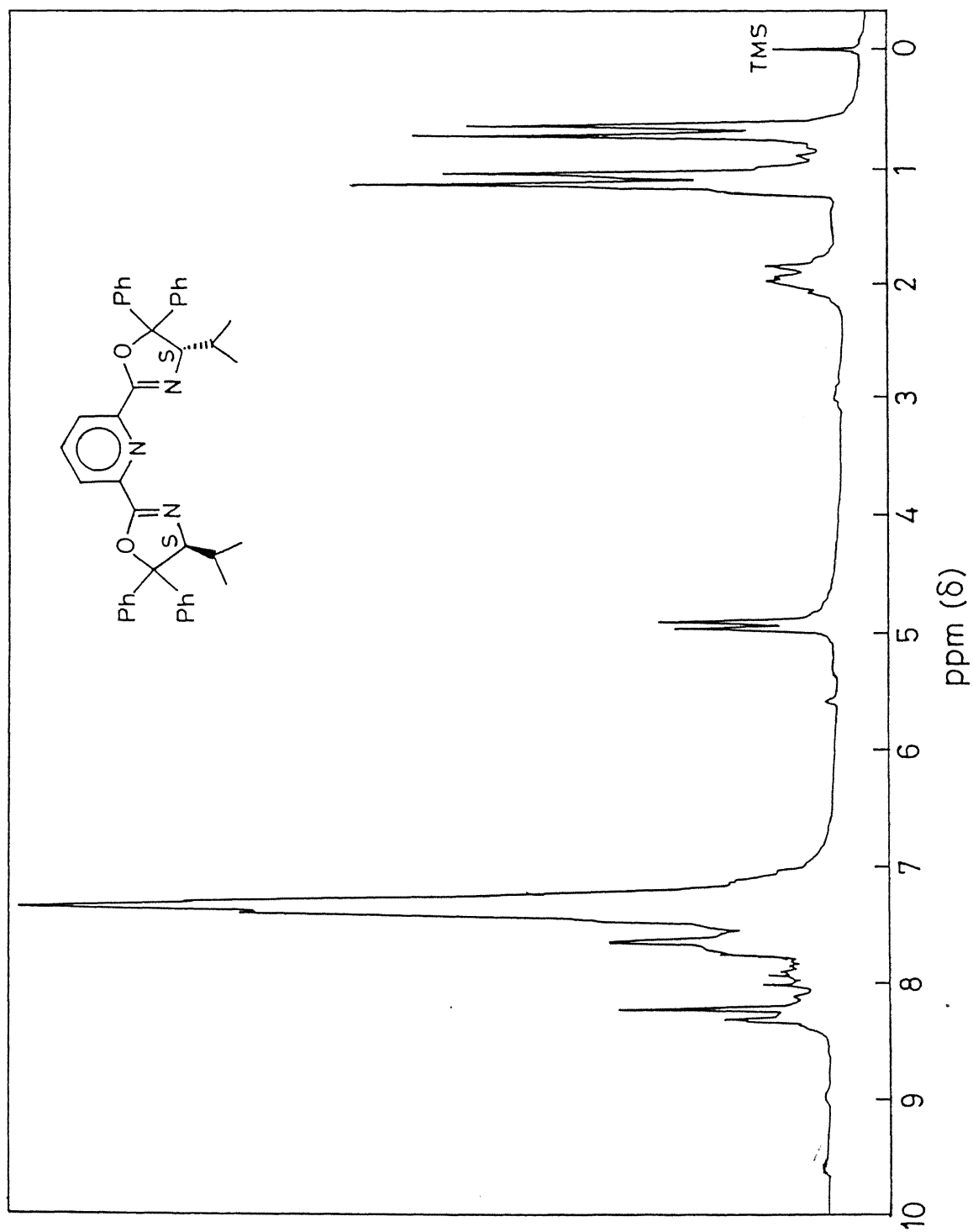
In this case, the peaks corresponding to *trans* - and *cis* -isomers, **39c** and **40c**, did not separate in ^1H NMR. So neither the diastereoselectivity, nor the enantioselectivity could be determined.

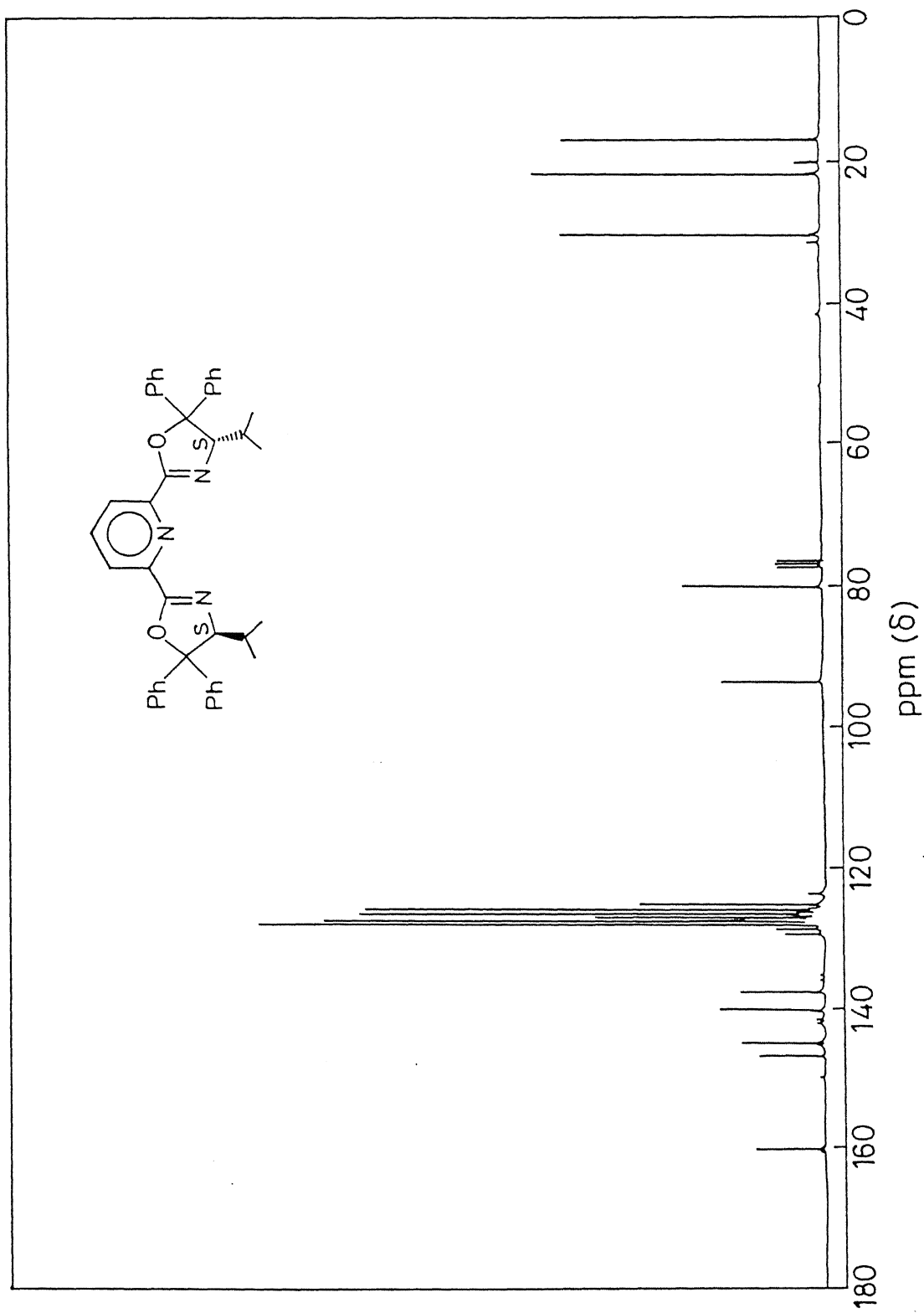


60 MHz ^1H NMR spectrum of (S)-27a in CCl_4 .

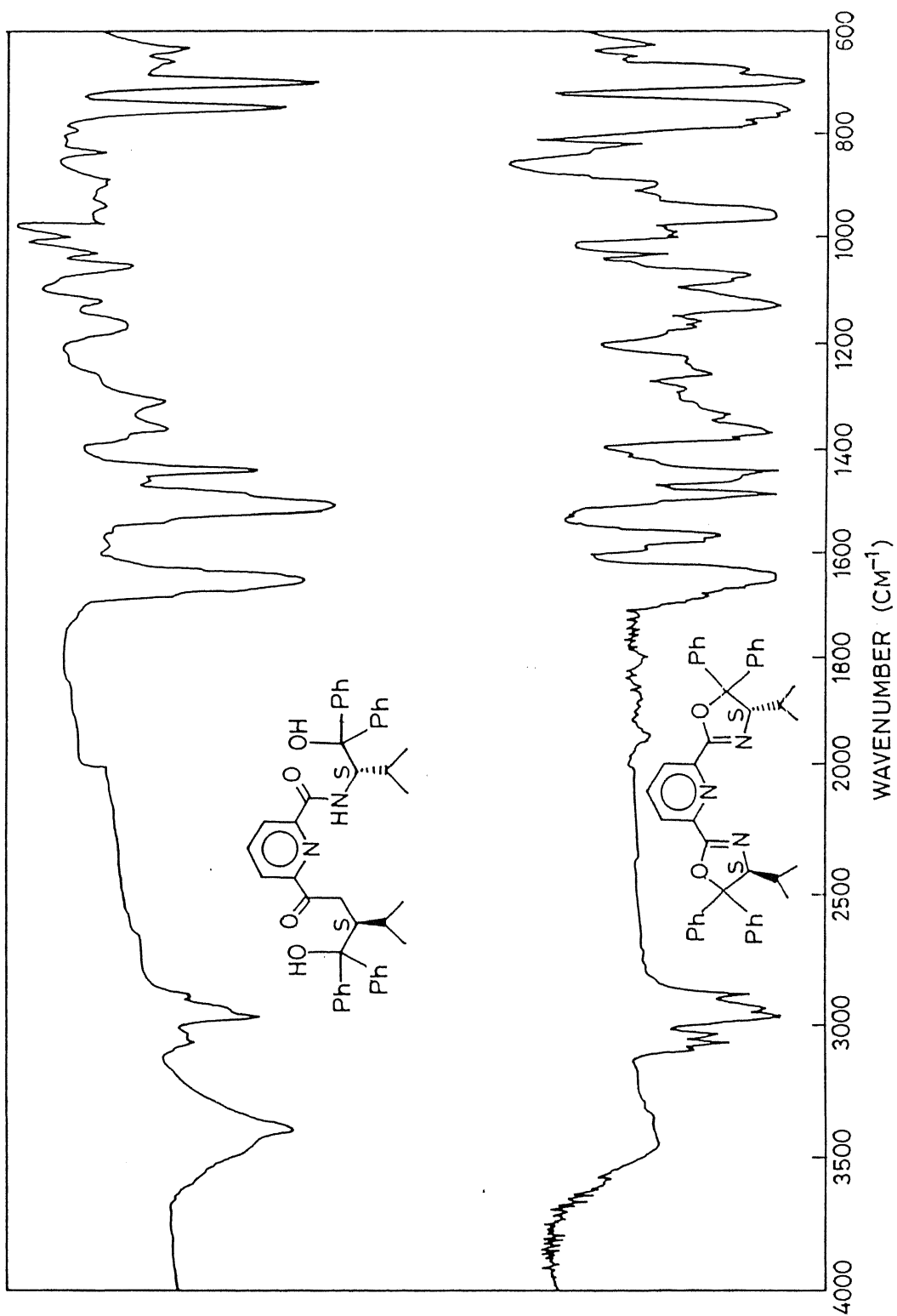


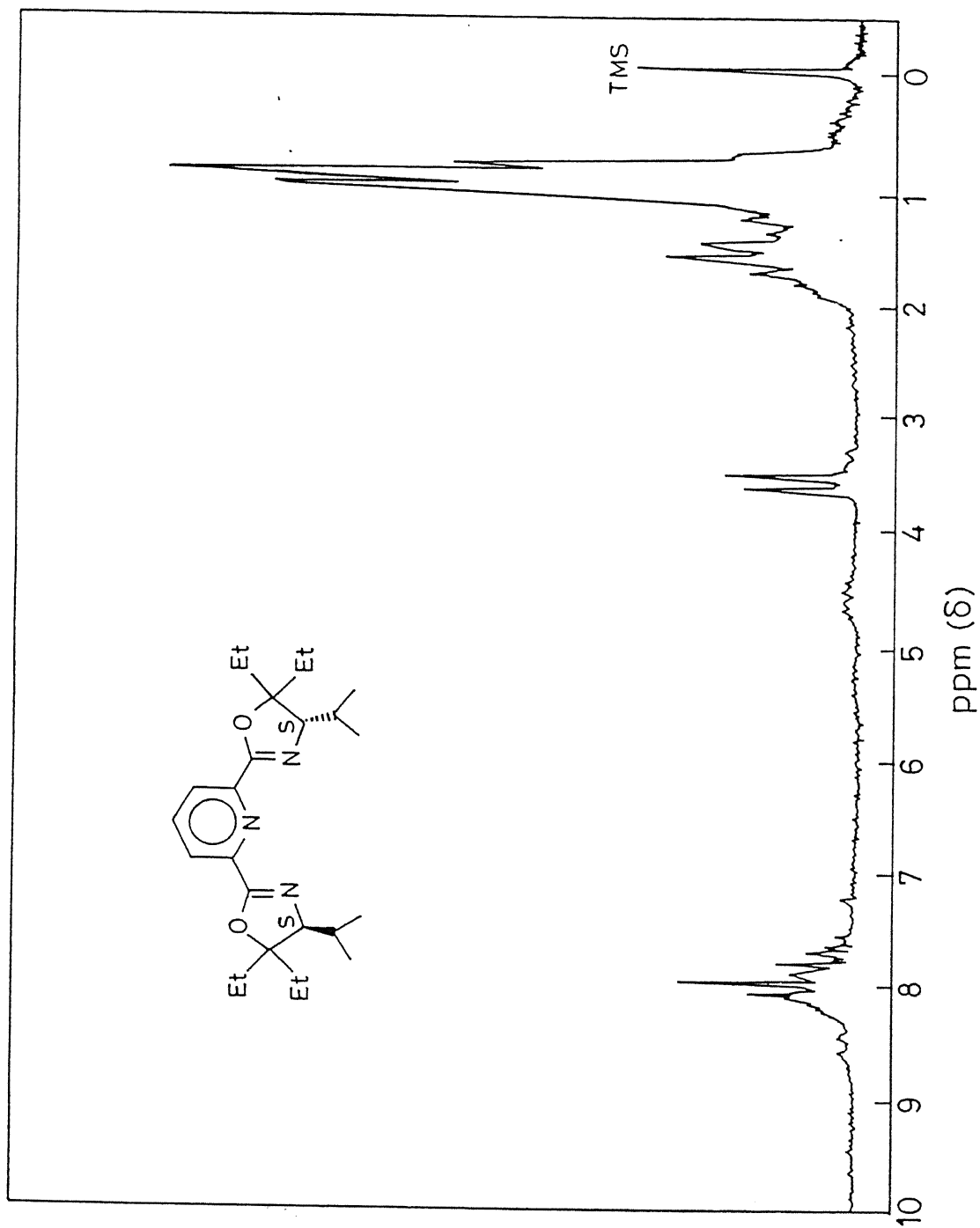
80 MHz ^1H NMR spectrum of **28a** in CDCl_3 .

80 MHz ^1H NMR spectrum of **29a** in CDCl_3 .

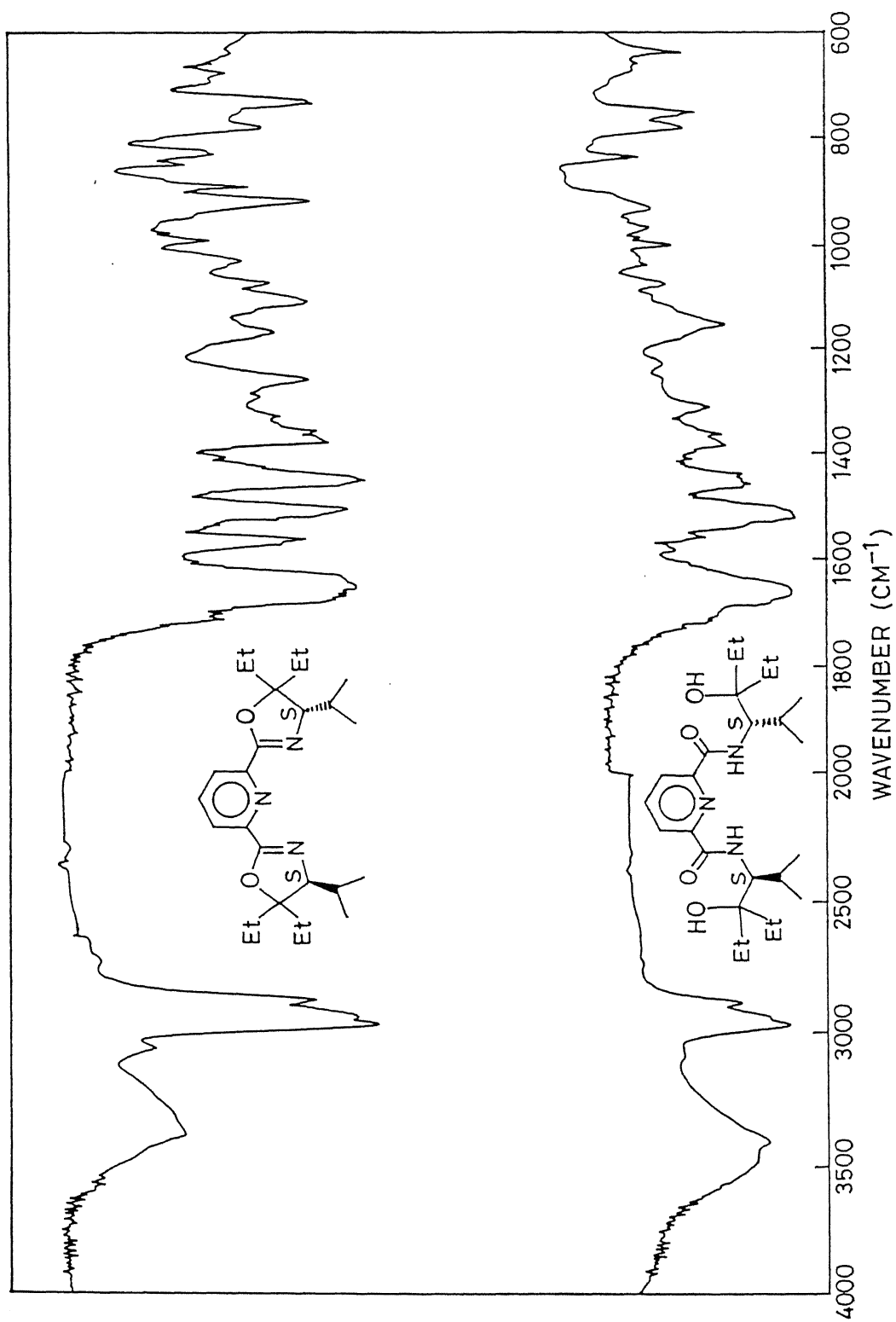


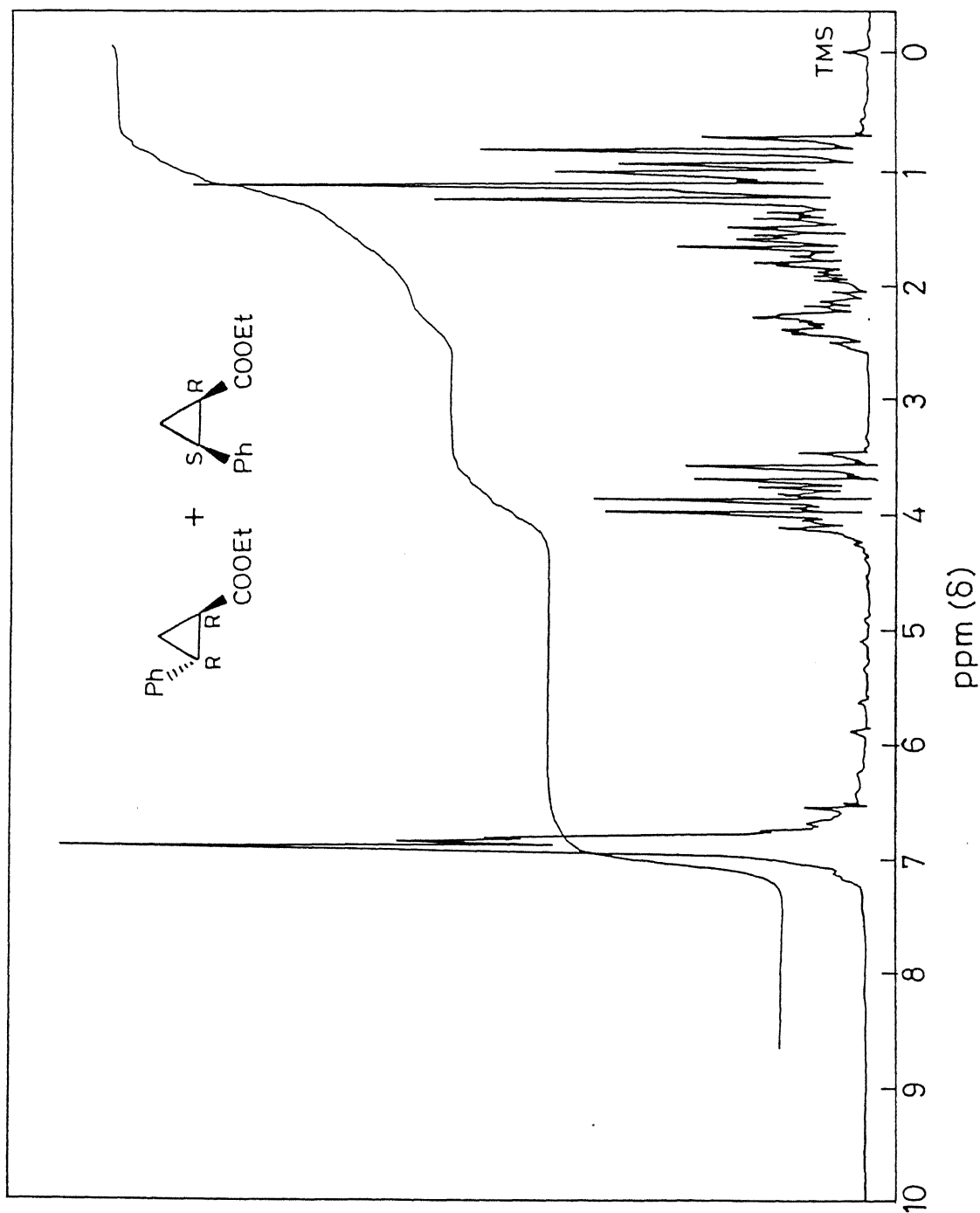
75.469 MHz ^{13}C NMR spectrum of **29a** in CDCl_3 .

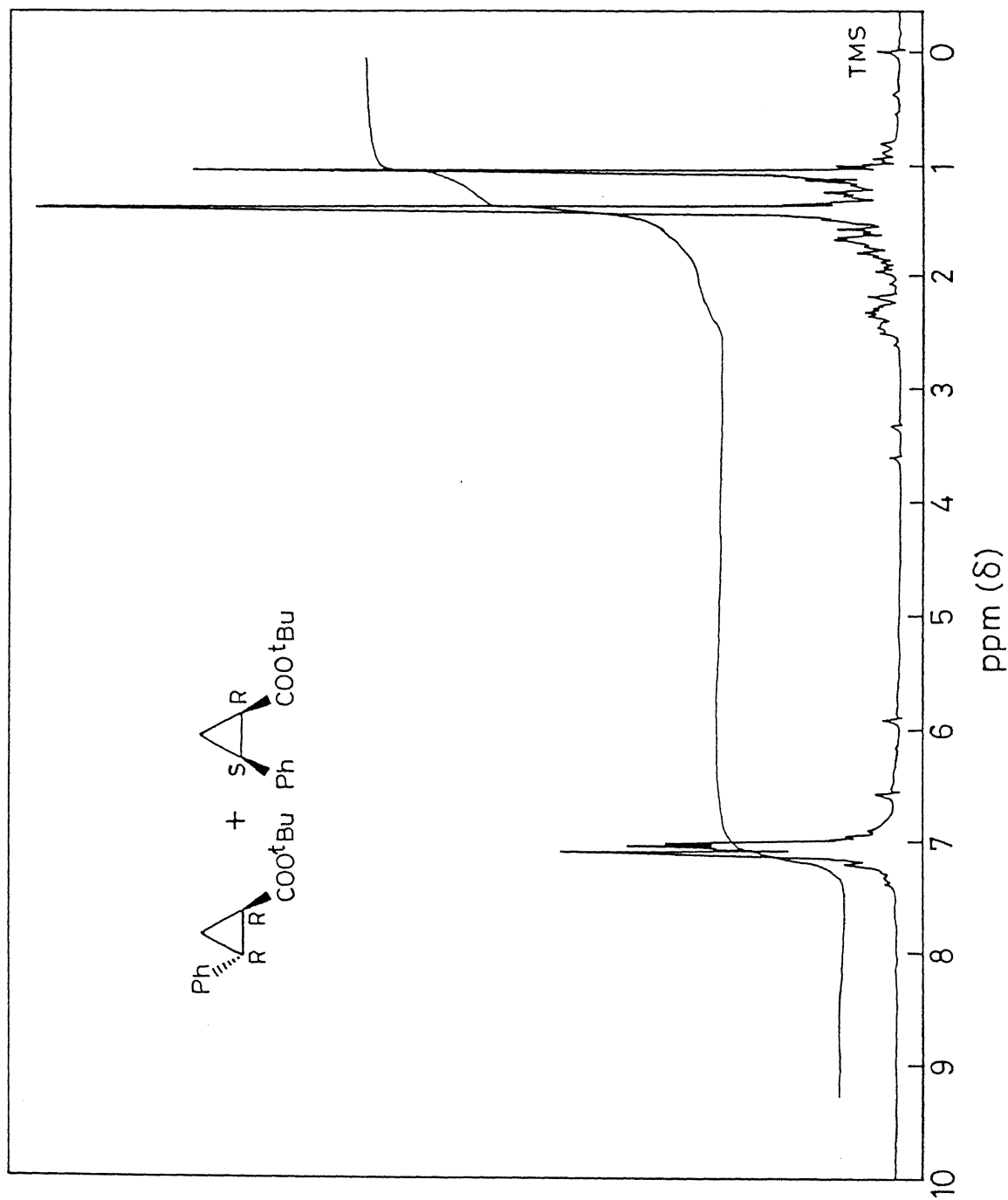


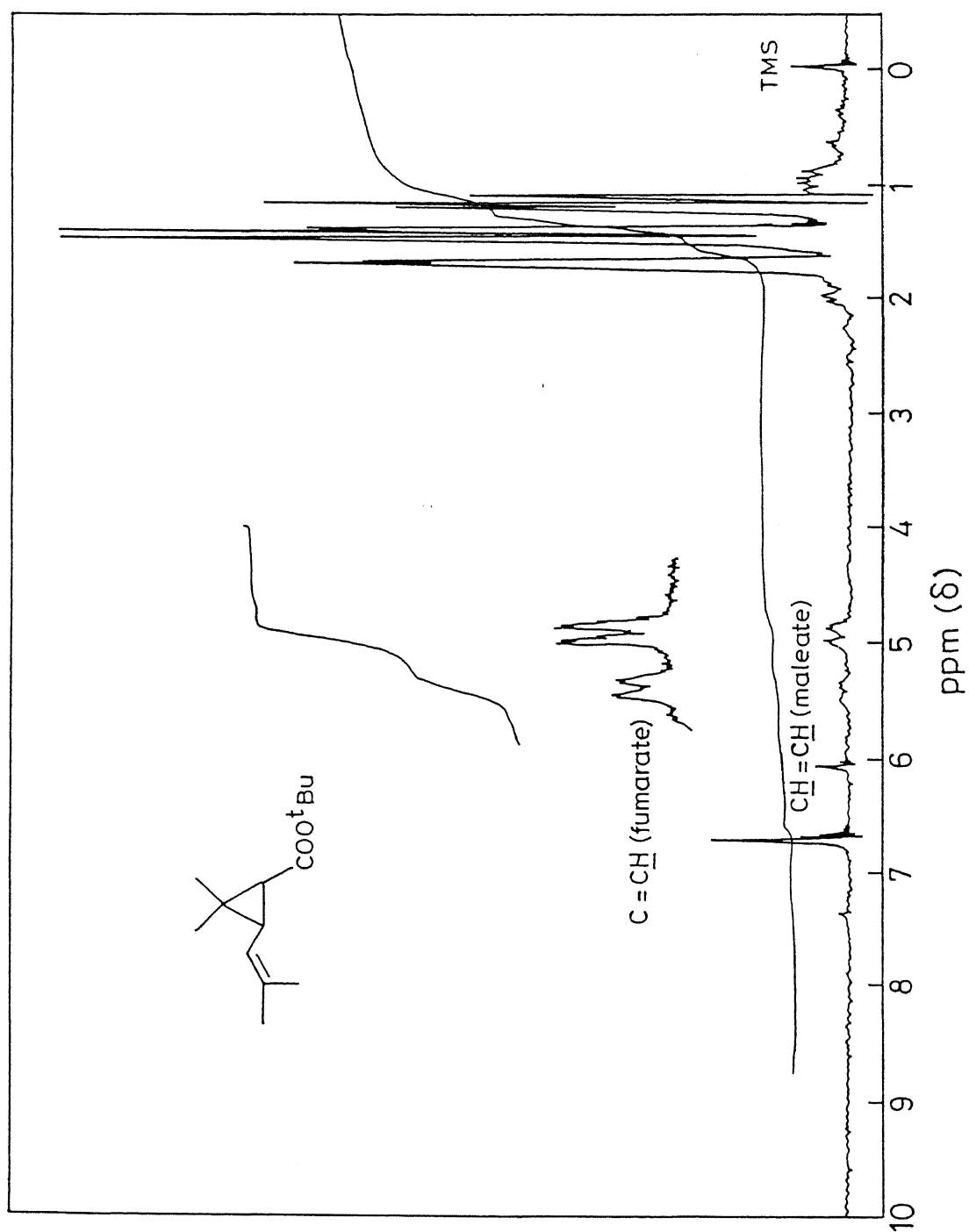


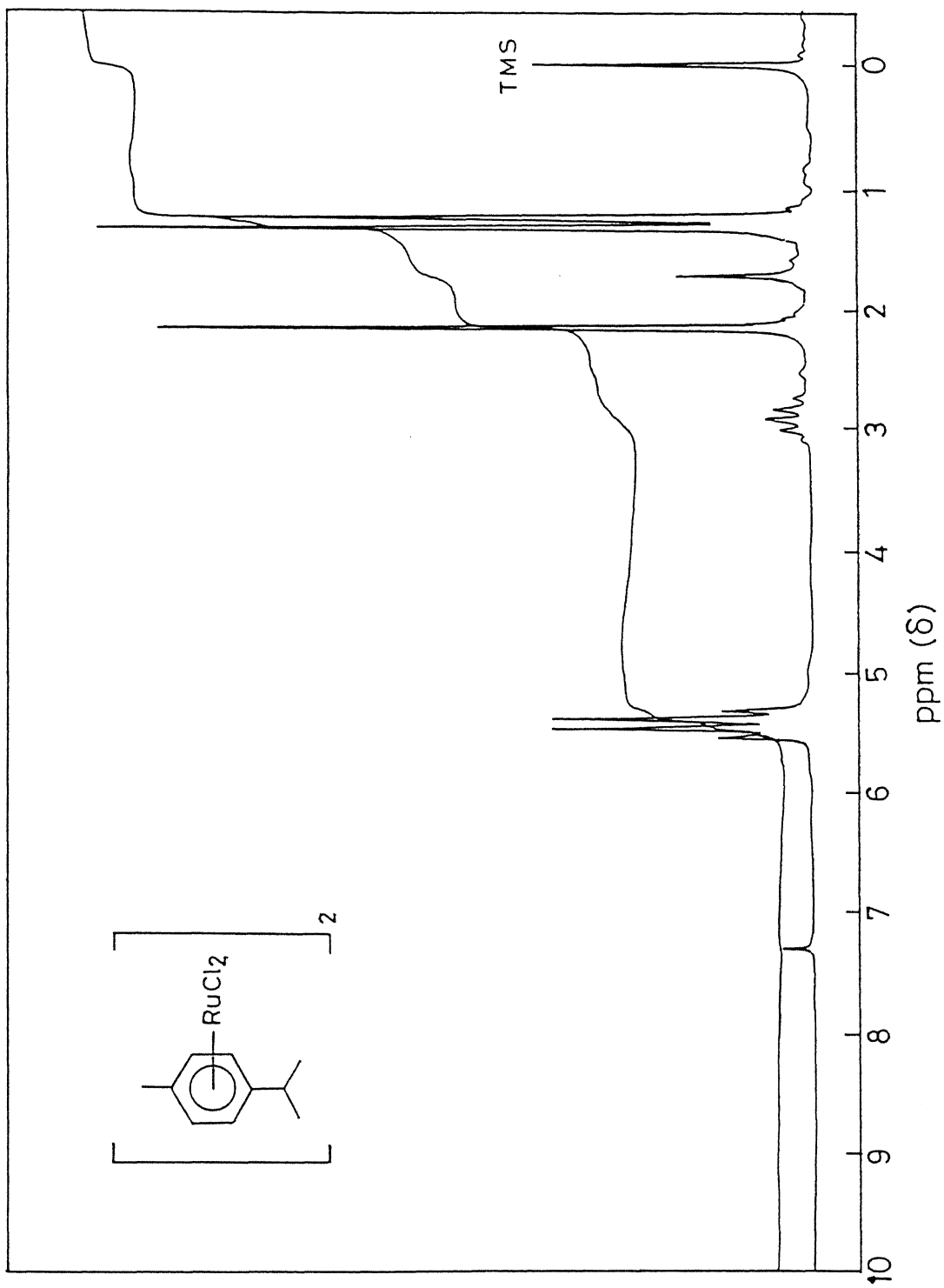
60 MHz ^1H NMR spectrum of **29b** in CCl_4 .



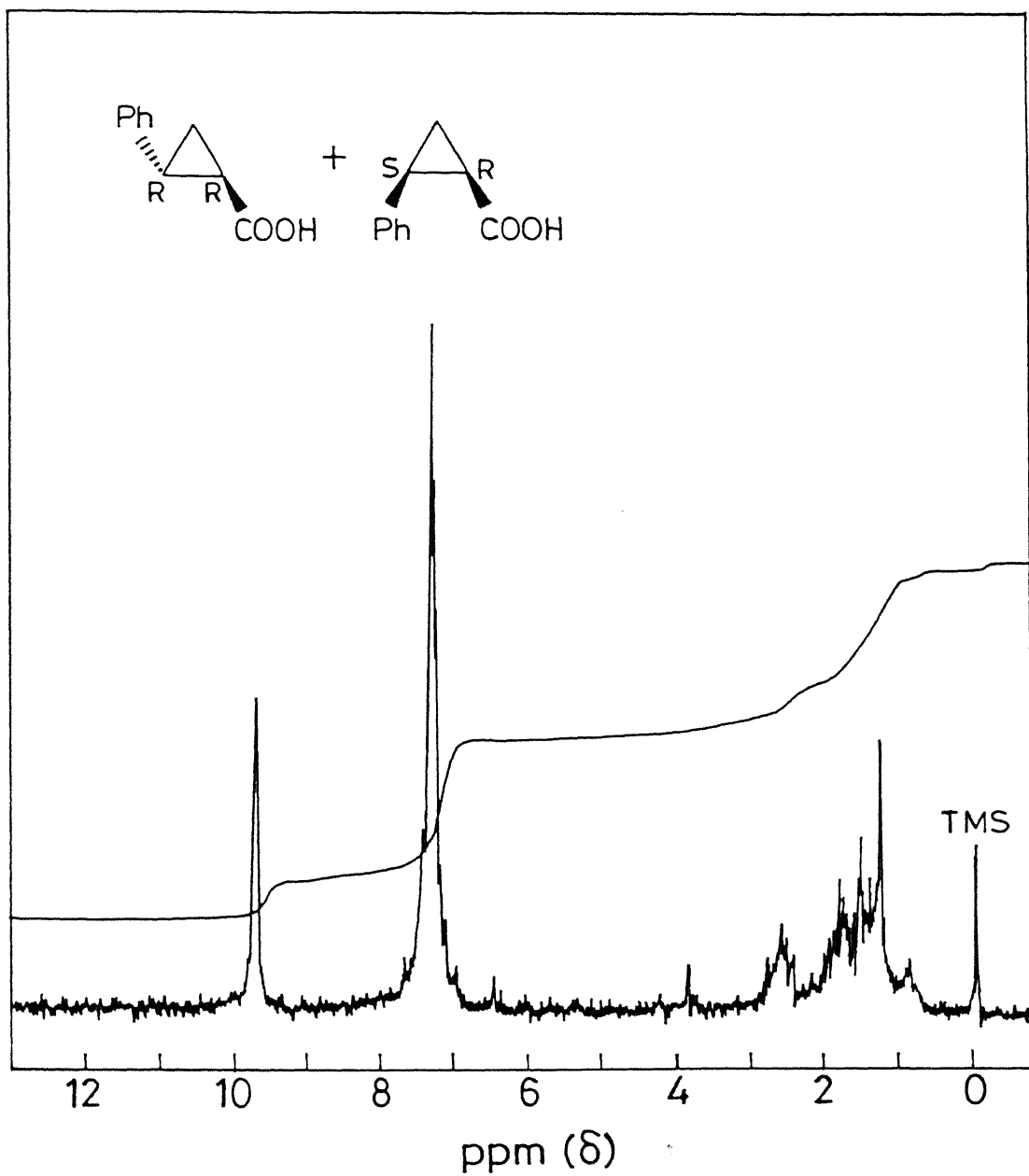
60 MHz ^1H NMR spectrum of 31a and 32a in CCl_4 .

60 MHz ^1H NMR spectrum of **35a** and **36a** in CCl_4 .

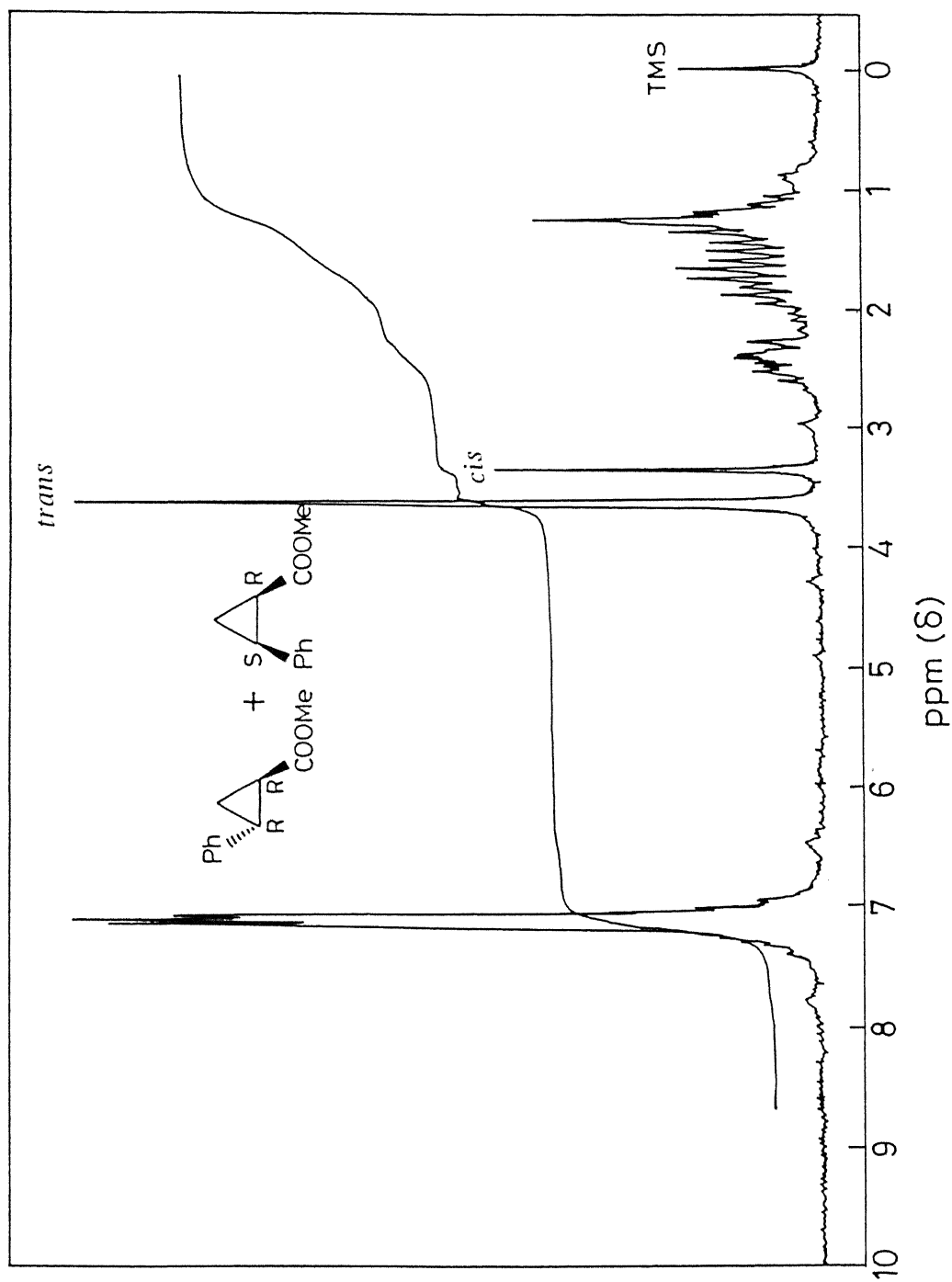
60 MHz ^1H NMR spectrum in CCl_4 .



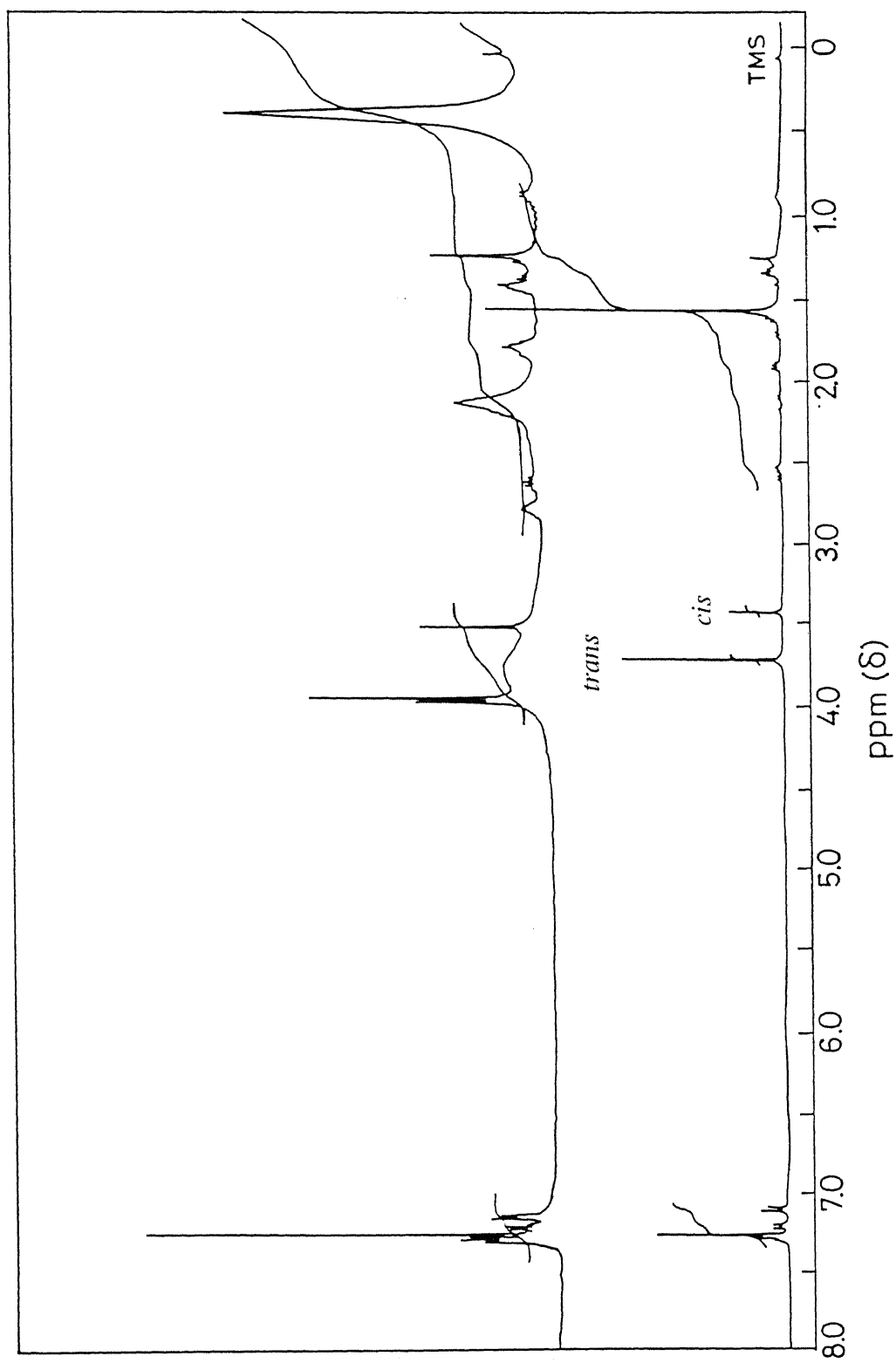
60 MHz ^1H NMR spectrum of **42** in CCl_4 .



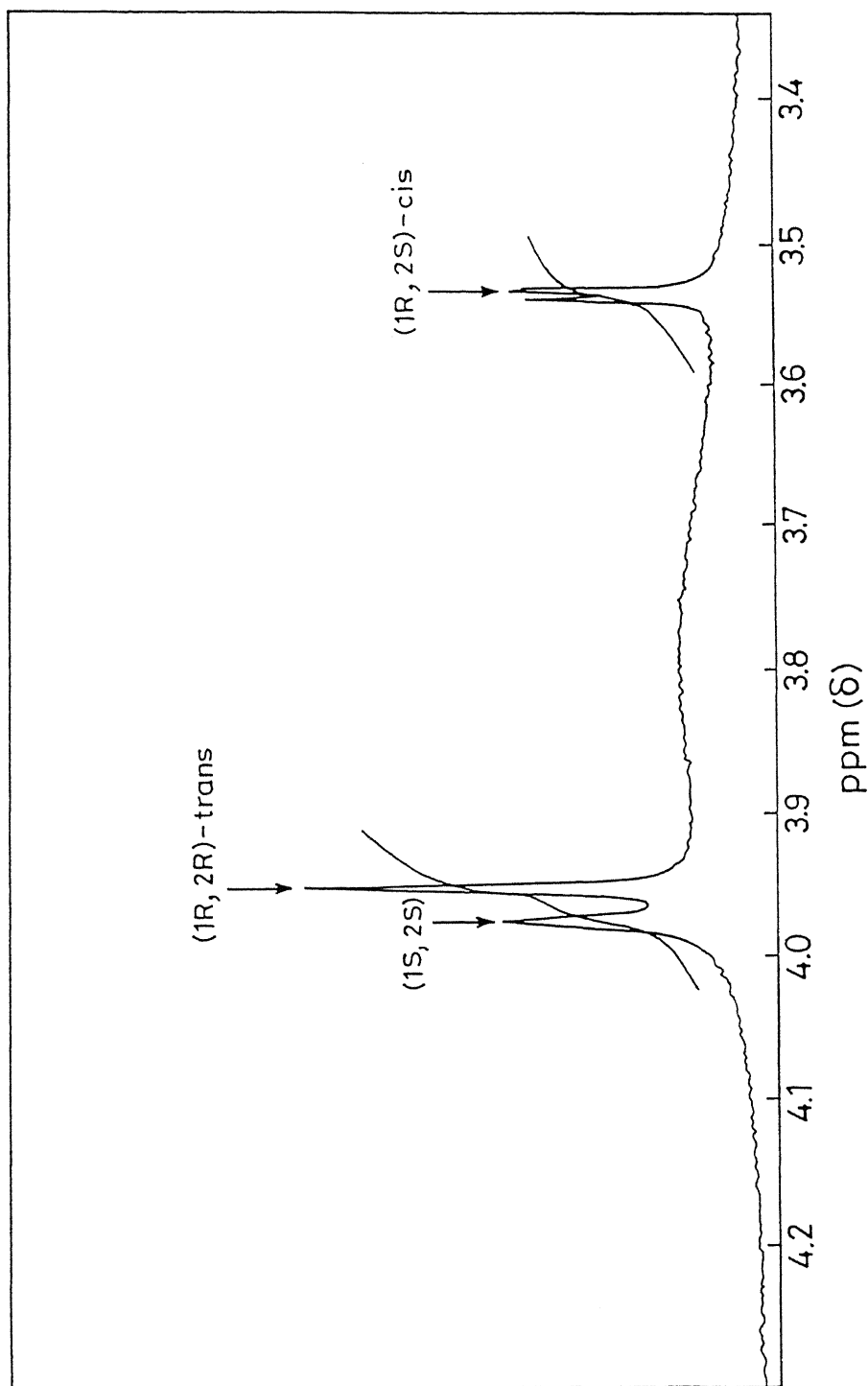
60 MHz ^1H NMR spectrum of **33** and **34** in CDCl_3 .



60 MHz ^1H NMR spectrum of **39a** and **40a** in CCl_4 .



400 MHz ^1H NMR spectrum of the shift reagent study of **39a** and **40a** using $\text{Eu}(\text{tfc})_3$ in CDCl_3 .



400 MHz: ^1H NMR spectrum of the shift reagent study of **39a** and **40a** using $\text{Eu}(\text{tfc})_3$ in CDCl_3 .

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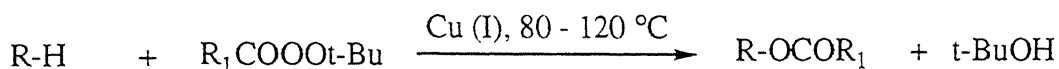
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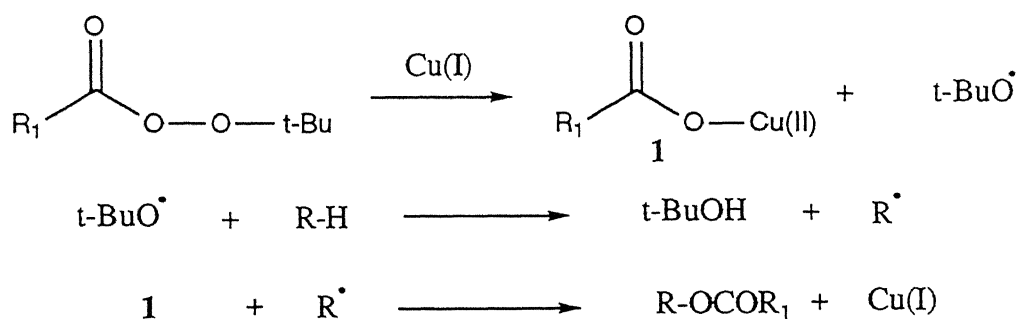
ENANTIOSELECTIVE ALLYLIC OXIDATION REACTIONS

A substrate containing activated hydrogen reacts with an organic peroxyester in the presence of a catalytic amount of metal salt (Cu or Co) to give esters. This reaction is popularly known as Kharasch reaction¹ (Scheme I).



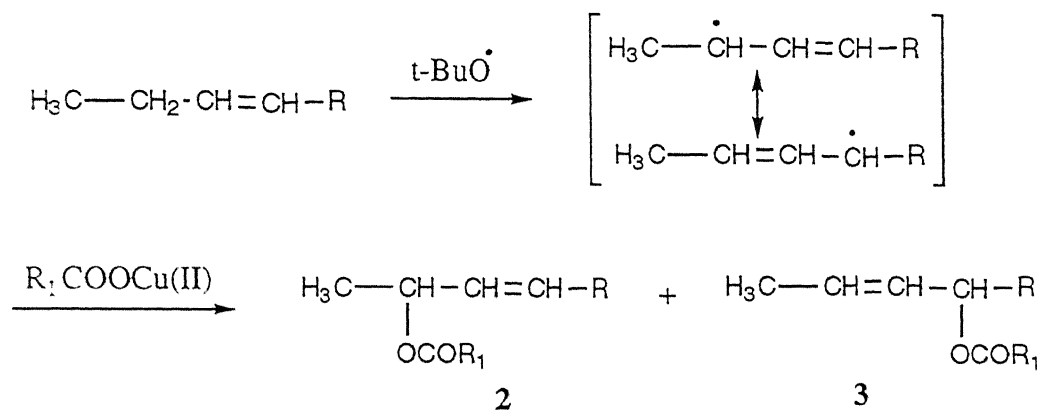
Scheme I

The facile decomposition of *tert*-butyl perbenzoate in the presence of copper salt made it possible to be utilized as synthetic reagent. The use of *tert*-butylhydroperoxide in the presence of carboxylic acid has been an alternative oxidant. The use of copper ion has two fold effects. Firstly, it increases the rate of decomposition of peroxyester. Secondly, it is the deciding factor for the composition of the end products, and in many cases, the products observed may differ from those of uncatalyzed reaction. The reaction mechanism involves three important steps: In the first step, there is a homolytic cleavage of the perester oxygen-oxygen bond by Cu(I) to generate benzoate anion and *tert*-butoxy radical. In the process, Cu(I) is oxidized to Cu(II) which reacts with benzoate anion to form Cu(II) benzoate 1.² In the next step, *tert*-butoxy radical abstracts the active hydrogen from the substrate to produce an alkyl radical.³ This radical then reacts with 1 to form the peroxyester, while Cu(II) is back to its original state which again enters the catalytic cycle (Scheme II).⁴



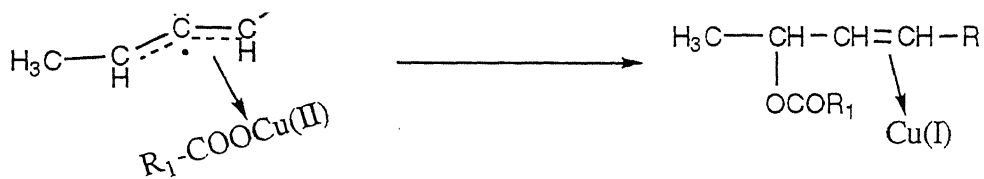
Scheme II

allylic systems. Thus, the direct functionalization of olefins exploiting the special nature of the allylic C-H bond occurs to bring about allylic oxidation reaction. Radical reactions with allylic compounds usually result in a mixture of isomeric products.^{5a} This is because the substrate radical R· may be represented by two contributing resonance structures. Consequently, hydrogen abstraction at an allylic carbon can result in either unarranged product **2** or rearranged product **3** as shown in scheme III.



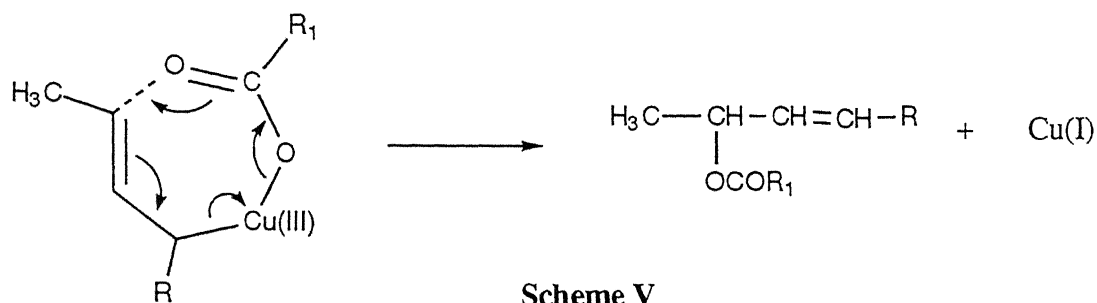
Scheme III

One of the remarkable features of these reactions is that under most conditions, the reaction of *t*-butyl perbenzoate and allylic compounds gives the thermodynamically least stable isomer **2** in considerable preference to the most stable isomer **3**.^{1,5b} So, terminal olefins were found to react with *tert*-butyl peresters in the presence of a copper salt catalyst yielding the unarranged secondary allylic esters in major amount. This fact provides evidence against the involvement of conventional free radical or carbonium ion intermediates which generally result in isomerization of the allylic system. This suggests that the displacement of the allylic hydrogen by the benzoyloxy group probably occurs in a concerted manner. So, there are two alternative proposals for this concerted mechanism.⁶ Firstly, there may be the specific interaction between the species **1** and the organic radical. The driving force for the selective formation of terminal olefin is provided by the incipient Cu(I)-alkene interaction which is more favoured by a terminal rather than an internal double bond (Scheme IV).



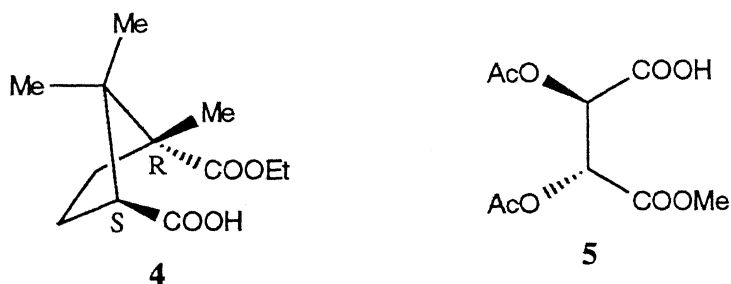
Scheme IV

The second proposal suggested an organocopper intermediate, involving a Cu(III) species in a pericyclic reaction. The rapid addition of Cu(II) to the allyl radical takes place to generate Cu(III) benzoate with the bound allyl fragment.⁴ A bond between Cu(II) and a radical would be consistent with the paramagnetic nature of Cu(II). In view of a number of evidences in favour of the intermediacy of Cu(III) species in the formation of allylic esters,^{6,7} second proposal was found to be the most accepted one (Scheme V).



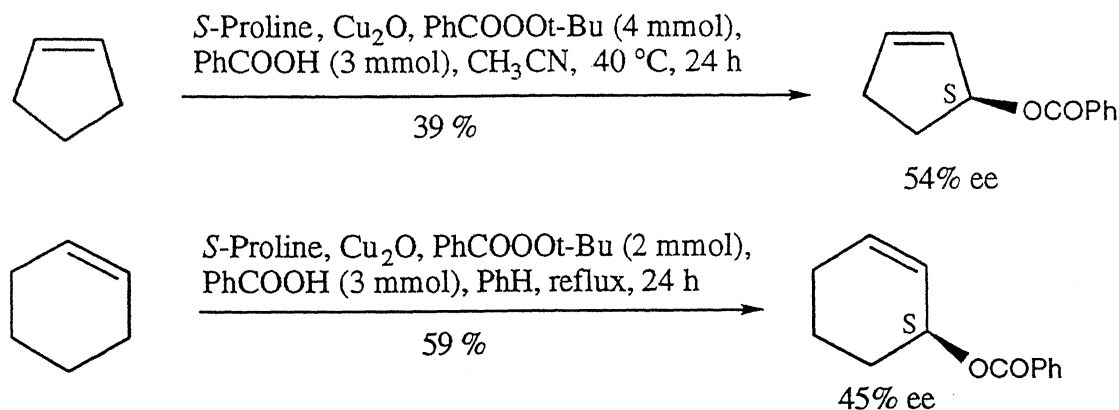
Scheme V

In 1965, D.B. Denney and coworkers⁸ reported the first asymmetric allylic oxidation using Kharasch reaction. They used stoichiometric amount of chiral copper complexes of (+)- α -ethyl camphorate **4** and di-O-acetyltartaric acid half-methyl ester **5** and carried out the reactions of different alkenes with *t*-butylhydroperoxide as oxidant. They achieved a maximum diastereomeric excess of 6-7%.



with *t*-butylperbenzoate using catalytic amount of optically active Cu-complex of a schiff base or an aminoacid in the presence of acetic acid. 2-Cyclohexenyl acetate with $[\alpha]_D = -23.7^\circ$ was produced in 16-17% enantiomeric excess. This was the first catalytic enantioselective allylic oxidation reaction.

In 1991 J.Muzart¹⁰ carried out the asymmetric allylic oxidation of cyclohexene using catalytic amount of aminoacids as chiral promoters. Among all the aminoacids, *S*-proline turned out to be the best. He tried the reaction in two different conditions. In the first condition 'A', he used *t*-butylhydroperoxide as the oxidant with acetic acid, in benzene as a solvent. In the second condition 'B' acetonitrile was the solvent. In both the cases, Cu(OAc)₂ was used as the copper salt. Under the condition 'A', heating was required for the product formation and it was observed that in order to get maximum asymmetric induction during the reaction, at least 4 equivalent of aminoacids per Cu(OAc)₂ was necessary. In this way a maximum of 28% ee for (*S*)-2-cyclohexenyl acetate was estimated during the oxidation of cyclohexene. On the other hand, under the condition 'B', 30% ee was obtained using slightly more than the stoichiometric amount of chiral ligand (1.3 equivalent with respect to Cu). They obtained the same sense of asymmetric induction, as reported by Araki,⁹ which supports the similarity between the mechanisms of acyloxylation carried out with RCO₃*t*-Bu-Cu and RCO₂H-*t*-BuOOH-Cu. The detailed study of his work was disclosed in 1995.¹¹ They used Cu₂O along with various structural analogs of (*S*)-proline as the chiral catalysts. They tried the reactions under different conditions and the best results obtained are summarized in scheme VI.

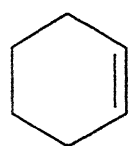


Scheme VI

So, under the conditions mentioned in the scheme VI, they obtained a maximum of 54% ee for (*S*)-2-cyclopentenyl-1-benzoate and 45% ee for (*S*)-2-cyclohexenyl-1-benzoate. Other cyclic alkenes gave poor yield (27 - 34% yield) and poor enantioselectivity (cycloheptene 23% ee; cis-cyclooctene 4% ee) during their oxidation to allylic benzoates. Two acyclic olefins such as 1-octene and allylbenzene were also used as substrates for allylic oxidation studies. In the case of 1-octene, a mixture of normal and rearranged products (4:1 ratio; 23% yield) was obtained and optical purity of the chiral compound was only 9%. Allylbenzene, on allylic oxidation, gave a mixture of normal and rearranged products (ratio 65 : 35) in 77% yield but there was no chiral induction in the reaction.

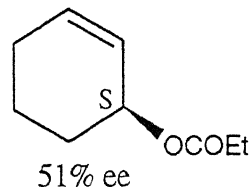
The solvents for allylic oxidation have to be aprotic, nonoxidizable and with suitable boiling temperature. The authors, in their studies showed the absence of any correlation between solvent polarity and enantioselectivity of the process. Besides acetonitrile and benzene, solvents like dichloroethane and sulfolane served good purpose. Invariably, acetonitrile gave better asymmetric induction compared to other solvents. The only exception was cyclohexene where benzene was superior (45% ee) to CH₃CN (39% ee). Among the different chiral promoters, they found (*S*) or (*R*)-proline to give the maximum ees. While the (*S*)-proline gave (*S*)- enantiomer of the allyl benzoate, (*S*)-N-methyl proline gave (*R*)-isomer of the allyl benzoate. They also varied the carboxylic acid RCOOH used for the reaction, and the data they obtained did not show any clear dependence between the enantioselectivity and the nature of the R group, except a weak increase in ee for aliphatic acids relative to aromatic ones. The best ee of 52% was obtained on using (CH₃)₃CCOOH in the case of cyclohexene. They also showed the dependency of enantioselectivity with nature of oxidant. It was found to decrease slightly in the following manner: *tert*-butylhydroperoxide ~ *tert*-butyl perbenzoate > cumylhydroperoxide.

In the same year, Feringa *et al.*¹² reported similar work by using several chiral Cu(II) complexes of cyclic aminoacids to catalyze the enantioselective allylic oxidation of cyclohexene to cyclohexenyl propionate. They reported that enhanced enantioselectivity (51% ee) was obtained for this reaction when copper bronze was also used and the reaction was done in the solvent mixture of propionic acid and acetonitrile (Scheme VII).



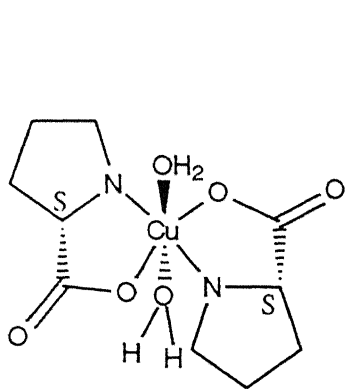
Cu bronze (5 mol%), $\text{PnCO}_3\text{-t-Bu}$, EtCO_2H ,
MeCN, 0 °C, 16 h

38% conversion

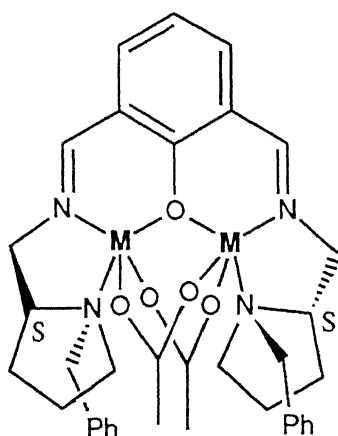


Scheme VII

The influence of the variation of a number of parameters was studied. Acetic acid in place of propionic acid gave only 35% ee in the above reaction. The use of CuOTf , $\text{Cu}(\text{OTf})_2$ and CuCN instead of $\text{Cu}(\text{OAc})_2$ lowered the enantioselectivity. When Zn was used instead of Cu bronze, 58% ee was achieved highlighting the role of metal as reducing agent in the catalytic cycle. The maximum enantioselectivity upto 61% ee was obtained on the use of 1,1-dimethyl propyl peroxyphthalate[$\text{t-BuCO}_3\text{-C}(\text{Me}_2)\text{Et}$] instead of t-butyl peroxybenzoate. Among different cyclic aminoacids as chiral ligands, (*S*)-proline turned out to be the best. Substitution at α -position of proline lowered the enantioselectivity. Also the variation of the ring size decreased the enantioselectivity in the following order: (*S*)-proline > (*S*)-azetidine-2-carboxylic acid > (*S*)-piperidine-2-carboxylic acid. The results obtained suggested the involvement of a chiral copper-proline complex. Structurally well defined bis-aquo-bis-(*S*)-prolinato- $\text{Cu}(\text{II})$ **6** gave similar results indicating the involvement of the same type of complex.

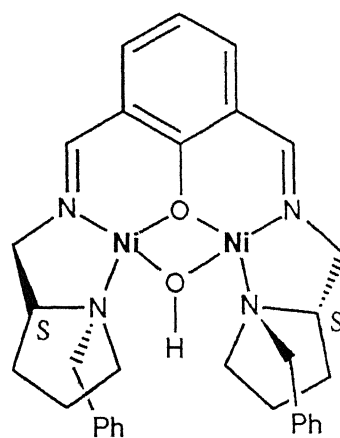


6



M = Ni(II), Cu(II)

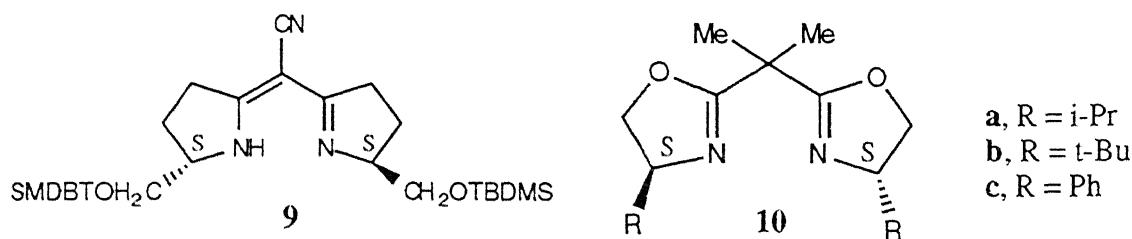
7



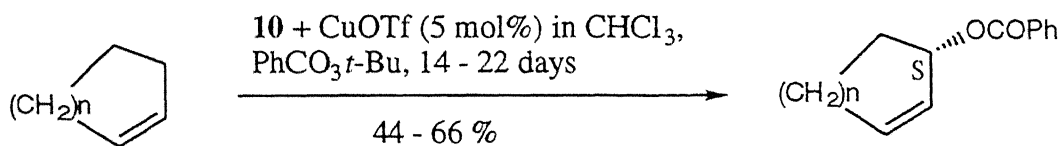
8

used in the oxidation of cyclohexene and allylbenzene with *tert*-butyl peroxyacetate (or -propionate), but only upto 10% ee was reached under the best condition.

Pfaltz *et al.*¹³ and Andrus *et al.*¹⁴ independently reported around the same time the use of copper complexes of chiral semicorrin and bisoxazoline type ligands in the enantioselective allylic oxidation of olefins. Pfaltz in connection with his work on chiral semicorrin-Cu complexes for enantioselective cyclopropanation of olefins found out that enantiomeric excess of 65-75% could be obtained with a stoichiometric amount of Cu(I) complex of the semicorrin ligand **9** for the reaction of cyclohexene with *tert*-butyl perbenzoate.¹⁵ The analogous catalytic reaction showed significant decrease in enantioselectivity. This prompted them to try bisoxazoline type ligands **10** for the same purpose. Copper complexes of these ligands have been used earlier in the asymmetric cyclopropanation reactions by Masamune and Evans independently (cf. chapter 1).



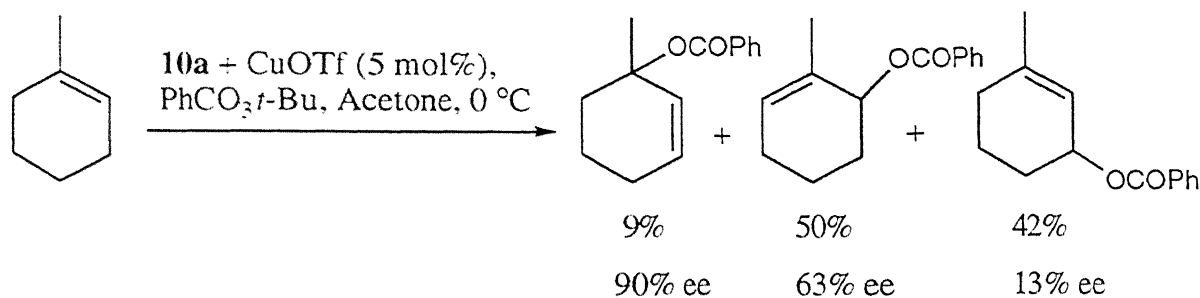
The Cu(I) complexes, prepared *in situ* from CuOTf or $[\text{Cu}^{\text{I}}(\text{MeCN})_4]\text{PF}_6$ and bisoxazolines **10**, showed good catalytic activity for allylic oxidation of cyclic olefins such as cyclopentene, cyclohexene, and cycloheptene using *tert*-butyl perbenzoate as oxidant.



n	Ligands	Solvents	Temp.	%ee
1	10a	Acetone	-20 °C	82%
1	10b	CH_3CN	-20 °C	84%
2	10b	CH_3CN	7 °C	77%
3	10a	CH_3CN	7 °C	82%

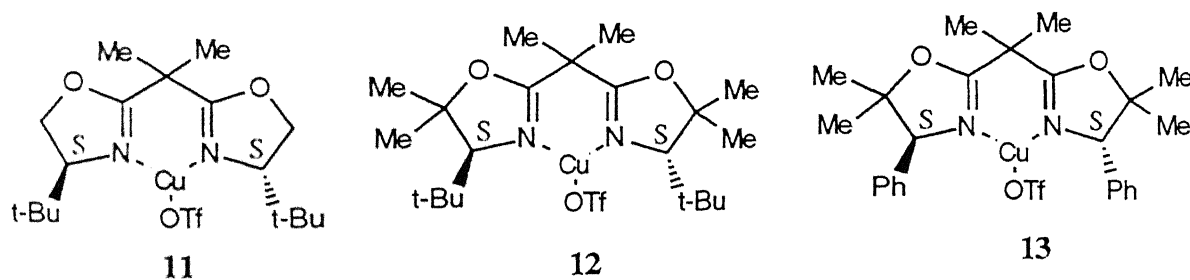
Scheme VII

cycloheptene to their corresponding (*S*)-allylic benzoates using the ligand **10a**. In the case of cyclohexene, the ligand **10b** gave a maximum of 77% ee. Depending upon a substrate and the specific ligand, either acetone or acetonitrile proved to be the solvent of choice. The reaction in acetone was generally faster than in acetonitrile. It is mentioned qualitatively that an analogous catalyst prepared from Cu(OTf)₂ is less reactive and less selective. The reaction was extended to 1-methyl cyclohexene which gave a mixture of three regioisomers and the results are shown in scheme VIII. The methyl group was not oxidized under these conditions.



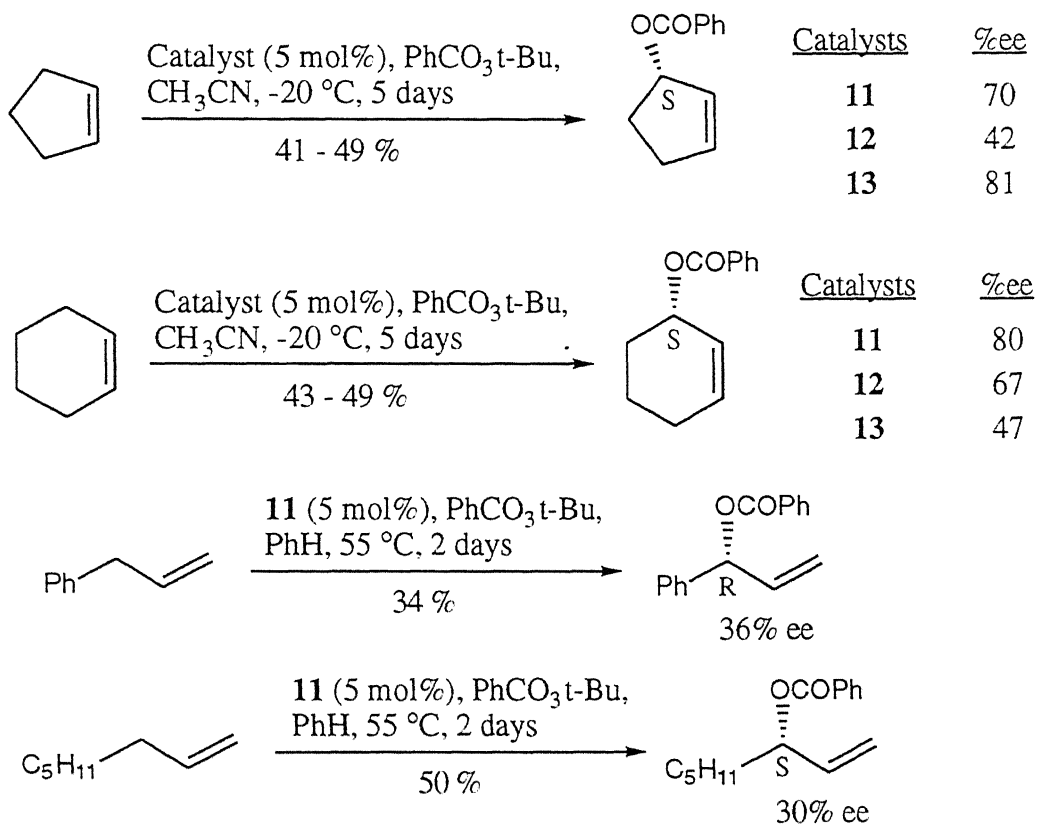
Scheme VIII

Andrus *et al.*¹⁴ independently published their results on allylic oxidation of olefins using isoxazoline-copper complexes **11**, **12** and **13**.



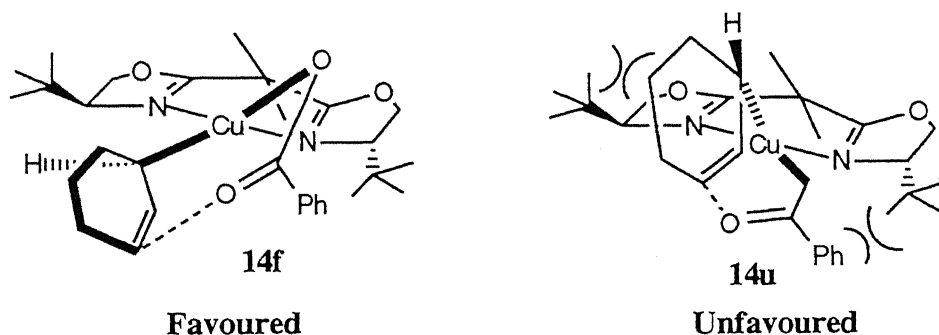
The best results for allylic oxidation with the above complexes have been summarized in scheme IX. Selectivity for cyclopentene was best, at 81% ee using the catalyst **13**. With cyclohexene the highest selectivity 80% ee was obtained using **11** as catalyst. It is reported that cyclooctene reacted at a much slower rate and with very poor selectivity (13% ee with **11**; 0% ee with **12**). Acyclic olefins were found to react with good yields in acetonitrile at 5 °C but the

were raised to 36 and 30% ee for allylbenzene and 1-octene (Scheme IX).



Scheme IX

The following model has been proposed by the authors to account for the stereoinduction in the above reactions.



In the favoured transition state (**14f**), the allyl and benzoate groups are linked to Cu in such a way so as to minimize the interaction with the flanking tert-butyl groups of the ligand. The

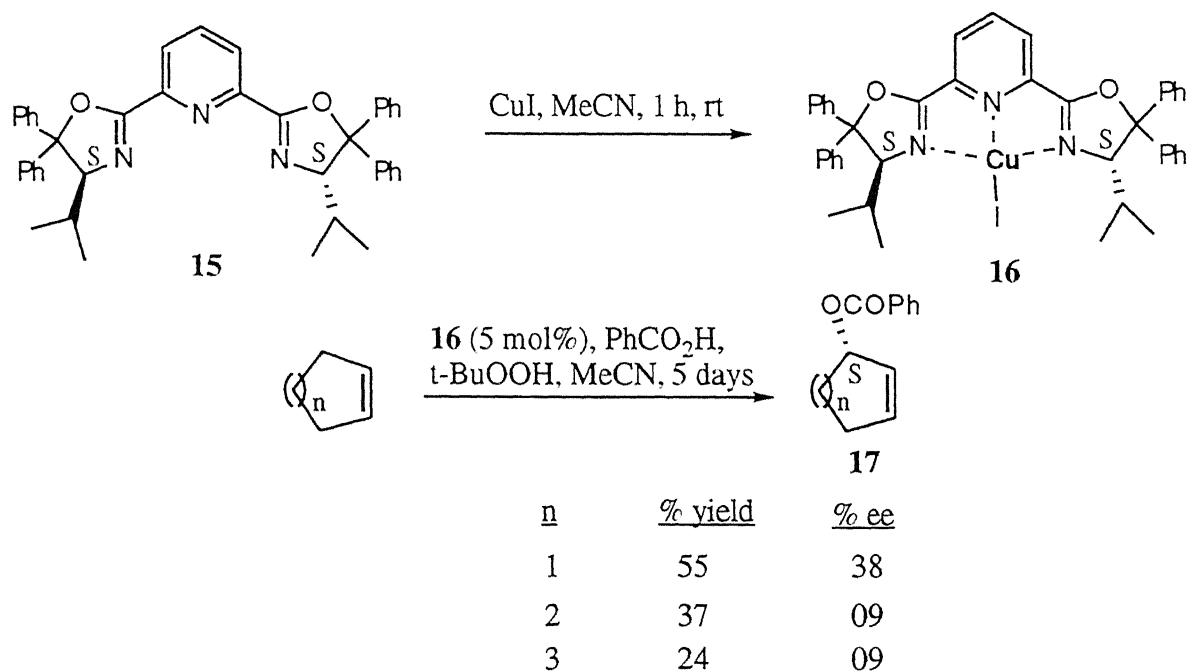
Cu(III) intermediate thus adopted a distorted square planar geometry placing the allyl and benzoate groups above or below the plane of the copper bisoxazoline ring. Then, the rearrangement takes place with the benzoate being delivered to the olefins. The authors further proposed that the lower selectivities for the acyclic olefins was due to an extra degree of freedom for rotation which exposes the other face of the olefin.

We started the work in this area by end of 1994. In the coming section we will be describing our contribution to this area.

Background

Enantiopure alcohols are very important structural units for synthesis of biologically active compounds. The direct route to these units could be *via* enantioselective reduction of corresponding ketones.¹⁶ However this approach has not been very successful due to lack of enough steric biasness in the appendages of ketones. Another nonenzymatic way to prepare allylic alcohols is *via* enantioselective deprotonation of epoxides using chiral nonracemic lithium amide bases and in our laboratory, we have made good progress in this area (cf. chapter 3).¹⁷ The drawback with the method is that it is not catalytic and more than stoichiometric amount of ligands is needed. The other possible approach could be based on the well known Kharasch reaction¹ in which allylic oxidation of olefin takes place with *t*-butyl perbenzoate in the presence of a catalytic amount of copper salt. Allylic esters, thus obtained could be converted into allylic alcohols by hydrolysis or reduction method. Early attempts to develop asymmetric version of the reaction using copper camphorate complexes and copper salt with aminoacids gave very poor enantioselectivity.⁸⁻¹⁰ Recently Muzart reported a maximum of 54% ee during the oxidation of cyclopentene with *tert*-butyl perbenzoate or a mixture of *tert*-butyl hydroperoxide and benzoic acid in the presence of copper salt of *S*- and *R*- proline.¹¹⁻¹² As a part of our programme in the area of asymmetric synthesis, we have used the bis(oxazolinyl)pyridine (pybox) type ligands for asymmetric cyclopropanation reaction (cf. chapter-1).¹⁸ In this chapter, we describe our efforts towards the application of chiral nonracemic pybox type ligands in asymmetric allylic oxidation reactions.¹⁹

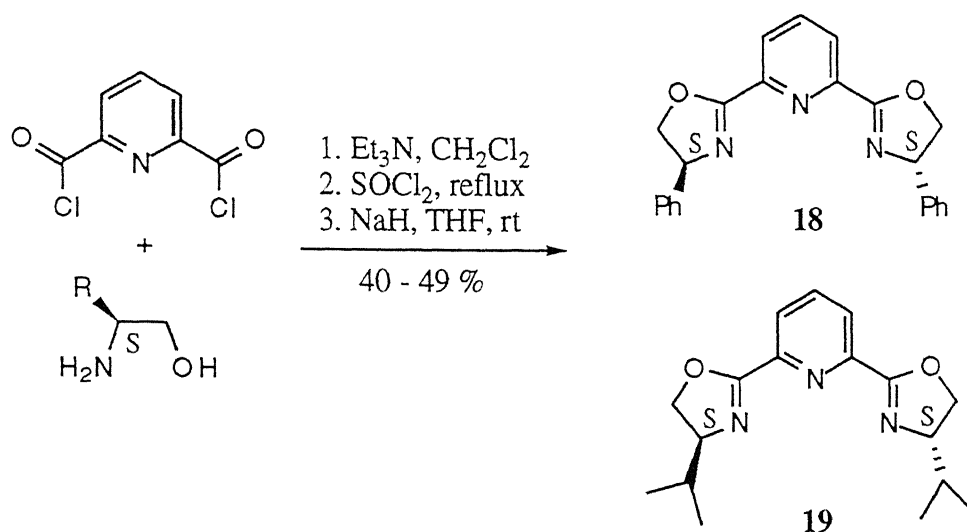
We envisioned that the chiral nonracemic pybox type ligand **15**¹⁸ complexed with Cu salt might be quite suitable as a chiral catalyst for asymmetric Kharasch reaction. In our initial study, we prepared the complex **16** as a red solid material by treating the **15** with CuI in acetonitrile. The ¹H NMR spectrum of the complex confirmed its C₂-symmetric nature. The catalyst **16** was used for the allylic oxidation of cyclic olefins in the presence of benzoic acid and tert-butyl hydroperoxide.



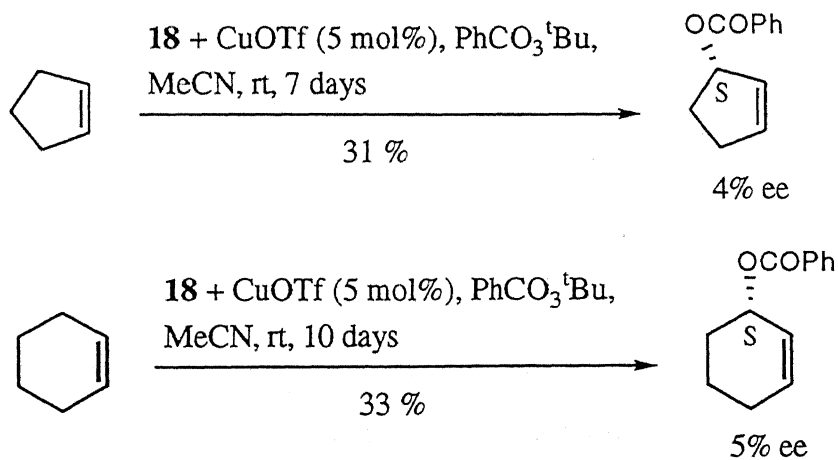
Scheme X

The results with the Cu-complex **16** are given above (Scheme-X). Some asymmetric induction (38% ee) in the case of cyclopentene prompted us to investigate the reaction further. We prepared several Cu complexes from the ligand **15** and other ligands such as **18** and **19**. We were mainly interested in the ligand **15** because we designed it with an aim of practicality in its preparation and purification. The presence of *gem*-diphenyl groups will make it more hydrophobic and purification over silica gel becomes easier. Besides, we could also see some stabilization of the transition states in the proposed reaction (*vide infra*). We synthesized these ligands from (*S*)-valine and (*S*)-phenylglycine. The synthetic steps for the ligand **15** are already discussed in the chapter 1. The ligands **18** and **19** were synthesized in three steps, viz., by coupling of 2,6-dipicoyl

chloride²⁰ and aminoalcohols, then refluxing with SOCl₂, followed by intramolecular condensation using NaH in THF.²¹

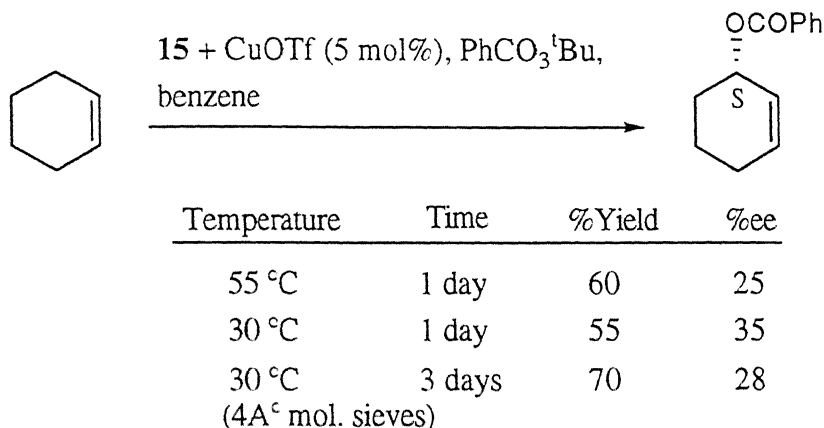


The ligand **18** complexed with CuOTf was applied, in the presence of *tert*-butyl perbenzoate as the oxidant, for the allylic oxidation of cyclopentene and cyclohexene. The Cu(I)triflate was prepared *in situ* from Cu(II)triflate by a reduction method with phenylhydrazine (PhNHNH₂). Phenylhydrazine reduced Cu(II) to Cu(I) and, in the process, phenyldiazene (PhN=NH) was formed which then decomposed to C₆H₆ and N₂.²² Unfortunately, the enantioselectivities obtained (Scheme XI) were very poor for both cyclopentene (4% ee) and cyclohexene (5% ee).



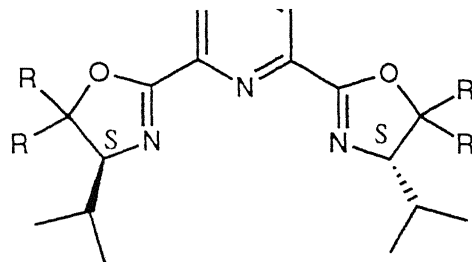
Scheme XI

using a complex of the chiral ligand **15** and Cu(OTf) prepared *in situ* as mentioned above. The reactions were done in various conditions and the results are summarized in scheme XII. The reaction was faster in benzene than in acetonitrile. Use of molecular sieves (4Å) in the reaction mixture increased the yield but there was not much effect in the enantioselectivity.



Scheme XII

After all these preliminary studies, the ligands **15** and **19** complexed with various copper salts were tried as catalysts. The allylic oxidation of a variety of olefins were carried out with 5 mol% of these catalysts under different conditions. All the reactions were done in acetonitrile and the results are summarized in table 1. In case of cyclohexene, the maximum selectivity obtained was 81% ee with CuOTf complex of the ligand **15** and *tert*-butyl perbenzoate as oxidant in the presence of 4Å molecular sieves (Entry 10). Variation of Cu salt had a major effect on the enantioselectivity in the reaction. Cu(I)triflate which was prepared *in situ* by a reduction method with phenylhydrazine proved to be the best. Both CuCN and Cu(OTf)₂ lowered the enantioselectivities to 42 and 52% respectively (Entries 11 & 12). Use of 4Å molecular sieves in the reaction flask had a pronounced effect on the enantioselectivity. It was observed that if the molecular sieves were not used, the enantioselectivity dropped to 70% (Entry 9). It was further noted that the ligand **15** gave better enantioselectivity than the ligand **19** (compare entries 8 and 10). The reaction was extended to other olefins. Cyclopentene showed the similar kind of behaviour during the oxidation reaction. In this case also, molecular sieves proved to be beneficial



15, R = Ph

19, R = H

Table 1: Asymmetric Catalytic Allylic Oxidation of Olefins with **15** & **19** in CH₃CN solvent at rt.

Entry	Olefin	Product	Ligand	Reagents ^a	Time (days)	Yield (%)	[α] _D (c 2-4, CHCl ₃)	% ee ^b
1.			19	Cu(OTf), PhCO ₃ ^t Bu	6	48	-86.4°	45
2.	"	PhOCO "	19	Cu(OTf), PhCO ₃ ^t Bu, 4A° mol. sieves	20	59	-107.5°	56
3.	"	"	15	Cu(OTf), PhCO ₃ ^t Bu	4	38	-80.8°	42
4.	"	"	15	Cu(OTf), PhCO ₃ ^t Bu, 4A° mol. sieves	4	70	-112.0°	59
5.	"	"	15	CuCN, PhCO ₂ H, ^t BuOOH	5	64	-88.6°	46
6.	"	"	15	Cu(OTf) ₂ , PhCO ₃ ^t Bu	2	28	-26.0°	14
7.			19	Cu(OTf) ₂ , PhCO ₃ ^t Bu	10	35	-24.5°	13
8.	"	"	19	Cu(OTf) ₂ , PhCO ₃ ^t Bu, 4A° mol. sieves	20	63	-84.0°	45
9.	"	"	15	Cu(OTf), PhCO ₃ ^t Bu	10	43	-127.9°	70
10.	"	"	15	Cu(OTf), PhCO ₃ ^t Bu, 4A° mol. sieves	15	58	-147.8°	81
11.	"	"	15	CuCN, PhCO ₂ H, ^t BuOOH	5	48	-77.5°	42
12.	"	"	15	Cu(OTf) ₂ , PhCO ₃ ^t Bu	5	48	-95.5°	52
13.			15	CuCN, PhCO ₂ H, ^t BuOOH	5	39	-11.5°	25

^aCu(I)OTf was prepared *in situ* from Cu (II) triflate and phenylhydrazine. ^b%ee was determined by 400 and 600 MHz ¹H NMR spectrum in the presence of chiral shift reagent Eu(hfc)₃ and by [α]_D comparison with the known values.

in enhancing the enantioselectivity. Thus, a maximum of 59% ee was obtained with Cu(OTf) complex of the ligand **15** and *tert*-butyl perbenzoate as oxidant in the presence of 4Å molecular sieves (Entry 4). Surprisingly, cycloheptene and cyclooctene under the above conditions gave messy products. However, when the reaction of cycloheptene was tried with benzoic acid and *tert*-butylhydroperoxide in the presence of CuCN complex of ligand **15**, the desired product was obtained, at best, in 39% yield but the asymmetric induction was poor. Acetonitrile was found to be a better solvent than benzene for cyclic olefins. (*S*)-Ligand was found to give (*S*)-allyl ester as the major product in all the cases.

There is enough evidence in the literature that the reaction proceeds *via* a radical intermediate. The Cu(I) cleaves the perester into benzoate anion and *tert*-butoxy radical.² The *t*-butoxy radical abstracts an allylic hydrogen to give *t*-butanol and an allylic radical.^{3a} It is proposed in the literature that the next step is rapid addition of Cu(II) to the allylic radical to generate Cu(III) benzoate which rearranges to the product *via* a six-membered intermediate.^{4,6} In view of our findings that Cu(OTf)₂ catalyzes the reaction equally well, it is unlikely that the above intermediate is formed, at least in the case of Cu(OTf)₂ as the Cu(II) has to go to Cu(IV) which is not a stable species. We assume that there is a coordination between the incipient double bond of the allylic radical and copper species.⁶ After the benzoate oxygen attacks the allylic carbon of olefin, the Cu species is reduced to the original oxidation state which enters the catalytic cycle of the reaction. A transition state model (Figure 1) is proposed to account for the stereoinduction in the reaction.

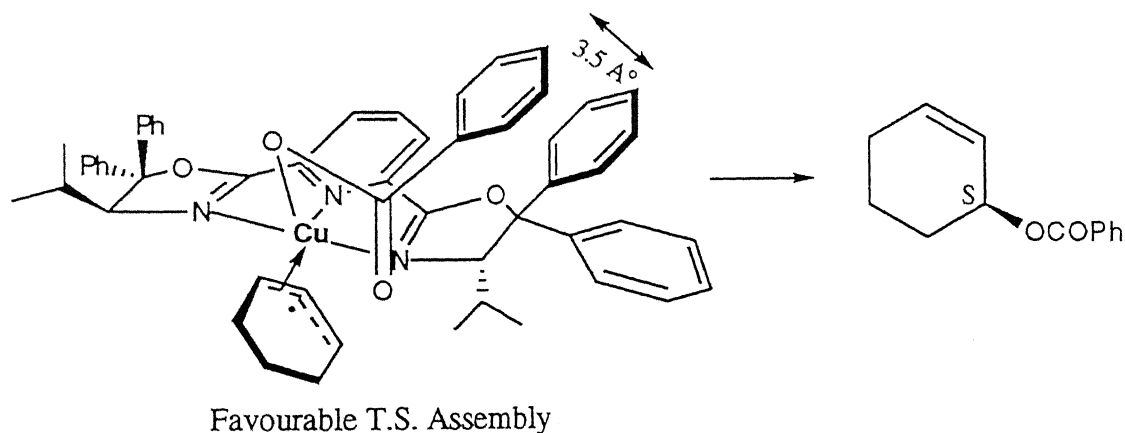


Figure 1

In this favourable transition state assembly, copper benzoate attains an orientation in such a way that there is π -stacking²³ of the two aromatic rings. Since the distance between both the rings is approximately 3.5 Å, there will be some attractive interaction which will stabilize the drawn conformation. In that case, allylic radical will approach the Cu species from the less hindered side as shown in the Figure-1. The benzoate oxygen attacks the allylic carbon which is electrophilic in nature due to the coordination of the incipient double bond with Cu species. This follows the reduction of Cu species into its original oxidation state. Thus, the catalytic cycle of the allylic oxidation of alkenes continues.

Conclusion

In conclusion, we have shown that copper complexes of the chiral bis(oxazolinyl)pyridine type ligands are good catalysts for allylic oxidation of olefins. In case of cyclohexene, we have achieved 81% ee which is highest to date, for this kind of reaction. Among all Cu salts, CuOTf was found to be the best. The effect of molecular sieves was quite important in enhancing the enantioselectivity of the reaction. The optical induction for other olefins is not very high.

Experimentals

General considerations

The common materials and methods have already been given in the experimental section of the chapter 1. The ligand **15** was prepared following our own procedure.¹⁸ The ligands **18** and **19** were prepared following the literature procedure.²¹ Cyclohexene, cyclopentene, cycloheptene, cyclooctene and *tert*-butylhydroperoxide were purchased from Fluka. Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato],europium(III), i.e., Eu(hfc)₃ was purchased from Aldrich. Benzoic acid and thionyl chloride were obtained from S. D. Fine Chem. Ltd. CuI, Cu(OTf)₂, and CuCN were Aldrich Chemicals. *tert*-Butyl perbenzoate was bought from Lancaster and phenylhydrazine was from Loba Chemie Pvt. Ltd.

Preparation of the complex 16: The pybox ligand **15**¹⁸ (500 mg, 0.826 mmol) and CuI (189 mg, 0.991 mmol) were taken in CHCl₃ (2 mL) under N₂ atmosphere. The whole reaction mixture was stirred for 1 h. Solvent was removed and the crude was filtered through silica gel column using 100% CHCl₃ to get the pure complex **16** (384 mg; yield 56%) as dark red solid; *R*_f 0.66 (1 : 20: EtOAc in CHCl₃); IR (KBr) 3060, 1645, 1445, 1185, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ0.62 (doublet, *J* = 6.6 Hz, 6H), 1.41 (split singlet, *J* = 5.4 Hz, 6H), 1.99 (m, 2H), 5.27 (broad singlet, 2H), 7.30 - 7.55 (aromatics, 20H), 8.12 (t, *J* = 9 Hz, 1H), 8.41 (d, *J* = 9 Hz, 2H); ¹³C NMR (CDCl₃, 75.469 MHz) δ16.38, 22.96, 29.94, 78.14, 95.65, 126.79, 127.87, 128.66, 138.65, 138.89, 142.97, 144.61, 161.05; MS (Fab, *m/z*): 668 (Ligand-Cu, base peak), 858 (Cu-Ligand-Cu), 1273 (Ligand-Cu-Ligand).

General Procedure for the Preparation of the Ligands, 18 and 19: These were prepared according to the literature procedure.²¹

To a mixture of (*S*)-aminoalcohol (11.75 mmol) and Et₃N (4.1 mL, 29.35 mmol) in CH₂Cl₂ (25 mL) was slowly added a solution of dipiconyl chloride²⁰ (1.20 g, 5.87 mmol) in CH₂Cl₂ (25 mL) at 0 °C. The reaction mixture was stirred for 1 day at room temperature. Organic layer was washed with water and brine. It was dried and concentrated. The crude solid amide was refluxed with excess SOCl₂ (15 equivalent) for 10 h. The unreacted SOCl₂ was removed under reduced pressure and the crude was taken in water, saturated with brine. The aqueous layer was

through silica gel column to get a solid product.

To a suspension of 3 equivalent of NaH in THF, was added a solution of the prepared solid compound in THF. The mixture was stirred overnight at room temperature and filtered through cotton. THF was removed. The crude mass was extracted with EtOAc, dried, and concentrated. Pure compound was obtained after column chromatography over silica gel.

2,6-bis[4'-(*S*)-phenyl oxazolin-2'-yl]pyridine 18: This was prepared as per the general procedure; Yield 40% as white solid; R_f 0.30 (100% EtOAc); $[\alpha]^{25}_D -180^\circ$ (c 1.3, CH_2Cl_2) [lit^{21b} $[\alpha]^{25}_D +185^\circ$ (c 1.03, CH_2Cl_2) for (*R,R*)-pybox ligand]; IR (KBr) 1645, 1570, 1450, 745. 700 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 4.40 (t, J = 9 Hz, 2H), 4.90 (dd, J = 11 Hz, 9 Hz, 2H), 5.46 (dd, J = 11 Hz, 9 Hz, 2H), 7.20 - 8.50 (aromatics, 13H).

2,6-bis[4'-(*S*)-isopropyl oxazolin-2'-yl]pyridine 19: This was prepared as per the general procedure; Yield 49% as white solid; R_f 0.36 (100% EtOAc); $[\alpha]^{25}_D -114^\circ$ (c 1.2, CH_2Cl_2) [lit^{21b} $[\alpha]^{25}_D -116.8^\circ$ (c 1.0, CH_2Cl_2)]; IR (KBr) 1650, 1470, 735 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.80 - 1.20 (m, 12H), 1.50 - 2.20 (m, 2H), 4.00 - 4.70 (m, 6H), 7.60 - 8.50 (m, 3H).

General Procedure for the Allylic Oxidation of Olefins using PhCOOH and *tert*-BuOOH: A solution of the ligand **15** (36.3 mg, 0.06 mmol) and Cu salt (CuI/CuCN) (0.05 mmol) in CH_3CN (4 mL) was stirred (rt / reflux temperature) for 1 h. To the red coloured solution, benzoic acid (305.3 mg, 2.5 mmol) followed by olefin (10 mmol) were added. Then, 70% *tert*-butylhydroperoxide (128.7 μL , 1 mmol) was added dropwise to the reaction mixture. The colour slowly changed from red to blue green. It was left for 5 days at room temperature. CH_3CN was removed and the crude was taken in EtOAc. Organic layer was washed with NaHCO_3 (twice) followed by water and dried. After solvent removal, it was purified over silica gel to get the allyl ester as the product.

General Procedure for the Allylic Oxidation of Olefins using $\text{Cu}(\text{OTf})_2$ and $\text{PhCO}_3t\text{-Bu}$: A solution of the ligand **15** (36.3 mg, 0.06 mmol) and $\text{Cu}(\text{OTf})_2$ (18 mg, 0.05 mmol) in CH_3CN (4 mL) was stirred at rt for 1 h. To this blue green solution, olefin (10 mmol) was added. Then, *t*-butyl perbenzoate (190 μL , 1 mmol) was added dropwise under N_2 and the

whole reaction mixture was left at room temperature till the reaction was complete. Completion of the reaction was indicated by the complete consumption of *t*-butyl perbenzoate (from tlc). Work up was done as above and the crude was chromatographed over silica gel to isolate allylic esters.

General Procedure for the Allylic Oxidation of Olefins using Cu(OTf) and PhCO₃*t*-Bu: A solution of the ligand (0.06 mmol) and Cu(OTf)₂ (18 mg, 0.05 mmol) in CH₃CN (4 mL) was stirred at rt for 1 h. Phenylhydrazine (6 µL, 0.06 mmol) was added and the colour of the solution changed from blue green to red [an indication for reduction of Cu(II) to Cu(I) species]. After 10 min of stirring (for the reactions to be carried out in benzene, CH₃CN was removed under vacuum and 4 mL benzene was added), olefin (10 mmol) was added, followed by dropwise addition of *tert*-butyl perbenzoate (190 µL, 1 mmol) under N₂. The reaction mixture was left at rt for the required time. Usual work up and purification gave allyl benzoates.

General Procedure for the Allylic Oxidation of Olefins using Cu(OTf), molecular sieves and PhCO₃*t*-Bu: A solution of the ligand (0.06 mmol) and Cu(OTf)₂ (18 mg, 0.05 mmol) in CH₃CN (4 mL) was stirred at rt for 1 h. Phenylhydrazine (6 µL, 0.06 mmol) was added and the colour of the solution changed from blue green to red [an indication for reduction of Cu(II) to Cu(I) species]. After 10 min of stirring (for the reactions to be carried out in benzene, CH₃CN was removed under vacuum and 4 mL benzene was added), a few grains of 4Å molecular sieves and olefin (10 mmol) were added, followed by dropwise addition of *tert*-butyl perbenzoate (190 µL, 1 mmol) under N₂. The reaction mixture was left at rt for the required time. After the completion of the reaction, it was filtered through cotton and worked up as above. Column chromatography gave allyl benzoates.

(*S*)-2-Cyclohexenyl-1-benzoate¹⁴ (Table 1; Entry 10): *R*_f 0.52 (2% EtOAc in petroleum ether); IR (neat) 3020, 2940, 1700, 1590, 1570, 1440, 1260 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.71 (m, 1H), 1.86 (m, 2H), 1.97 (m, 1H), 2.06 (m, 1H), 2.13 (m, 1H), 5.51 (broad singlet, 1H), 5.83 (m, 1H), 6.01 (m, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 2H).

With Eu(hfc)₃, the *ortho* protons of the benzoate shifted and separated in ¹H NMR spectrum (600 MHz). The relative intensities of the two peaks at δ 9.04 ppm (minor) and at δ 9.10 ppm (major) gave the enantiomeric excess of 79.5%. The optical purity of the shift reagent is

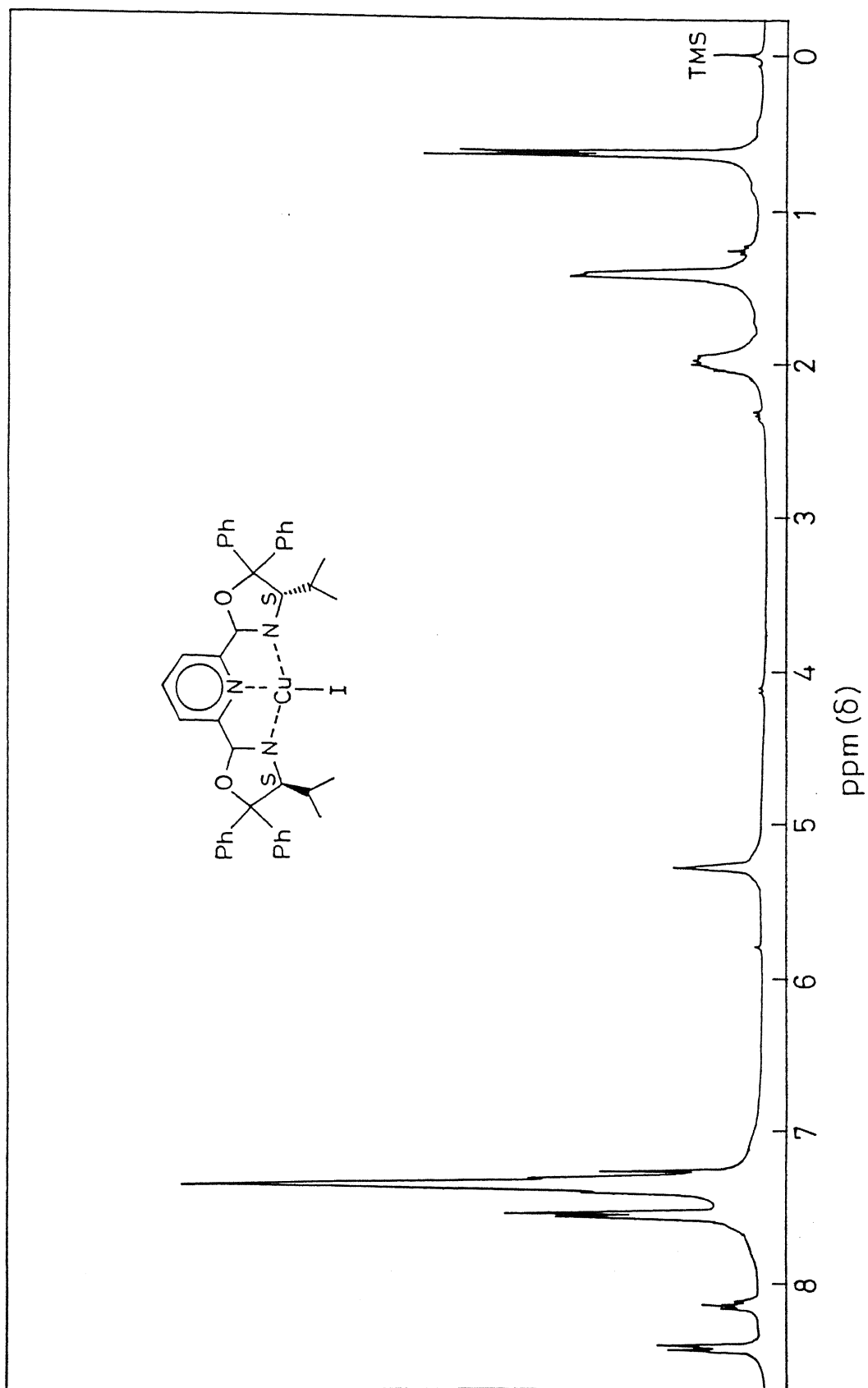
98%. So, corrected value of the optical purity of (*S*)-2-cyclohexenyl-1-benzoate is > 81% ee. This value also matched with the rotation data, $[\alpha]^{25}_{\text{D}} -147.8^{\circ}$ (*c* 3.9, CHCl_3), [lit^{11b} $[\alpha]^{25}_{\text{D}} -67^{\circ}$ (*c* 4.64, CHCl_3) for 37% ee].

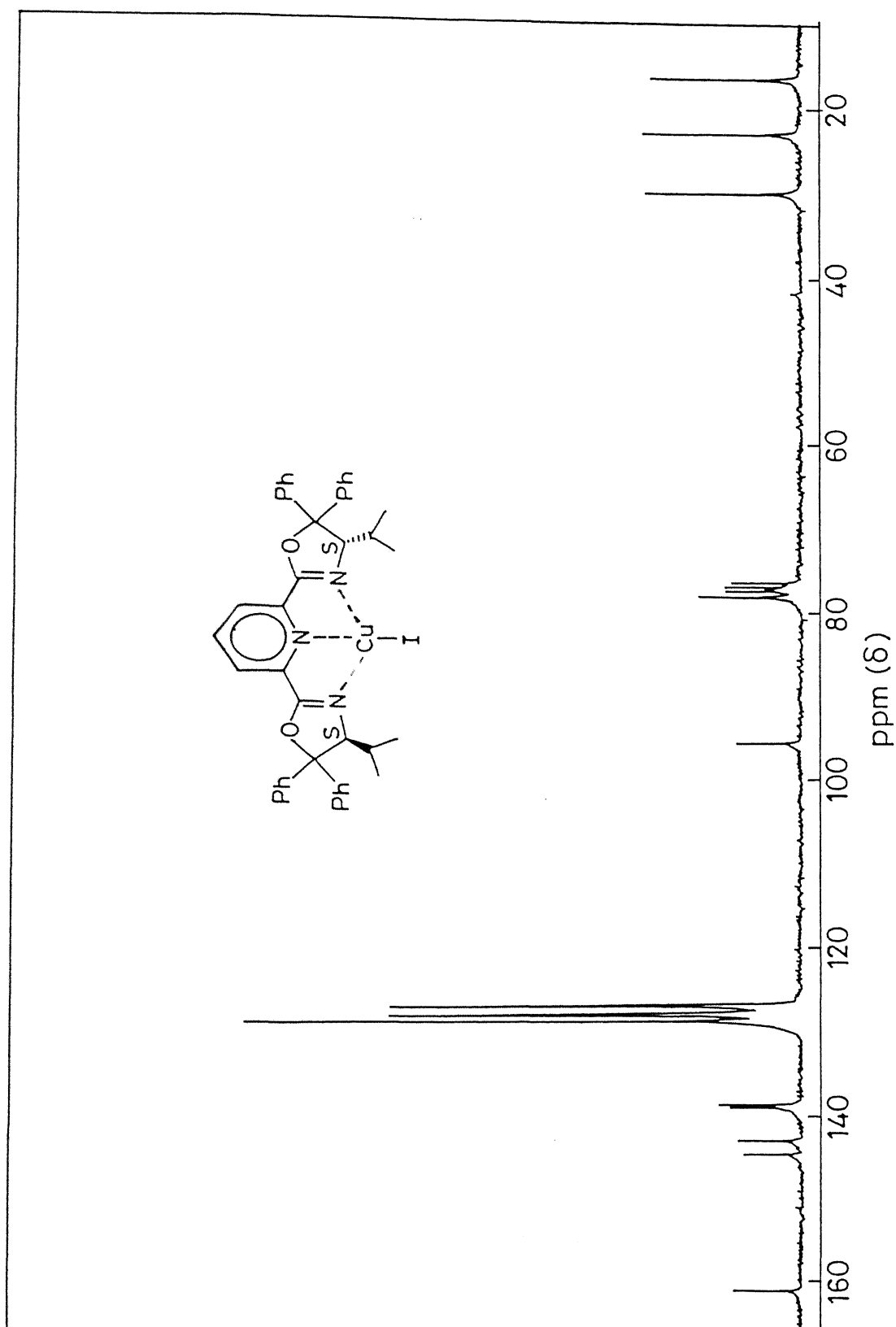
(*S*)-2-Cyclopentenyl-1-benzoate¹⁴ (Table 1; Entry 6): *R*_f 0.60 (2% EtOAc in petroleum ether); IR (neat) 3020, 1770, 1440 cm^{-1} ; ¹H NMR (CDCl_3 , 600 MHz) δ 1.96 (m, 1H), 2.37 (m, 2H), 2.56 (m, 1H), 5.93 (m, 2H), 6.13 (m, 1H), 7.38 - 7.53 (m, 3H), 8.00 - 8.08 (m, 2H).

With $\text{Eu}(\text{hfc})_3$, the *ortho* protons of the benzoate shifted and separated in ¹H NMR spectrum (600 MHz). The relative intensities of the two peaks at δ 9.70 ppm (minor) and δ 9.75 ppm (major) gave the enantiomeric excess of 14%. This value matched with the rotation data, $[\alpha]^{25}_{\text{D}} -26.0^{\circ}$ (*c* 2.0, CHCl_3), [lit^{11b} $[\alpha]^{25}_{\text{D}} -103^{\circ}$ (CHCl_3) for 54% ee].

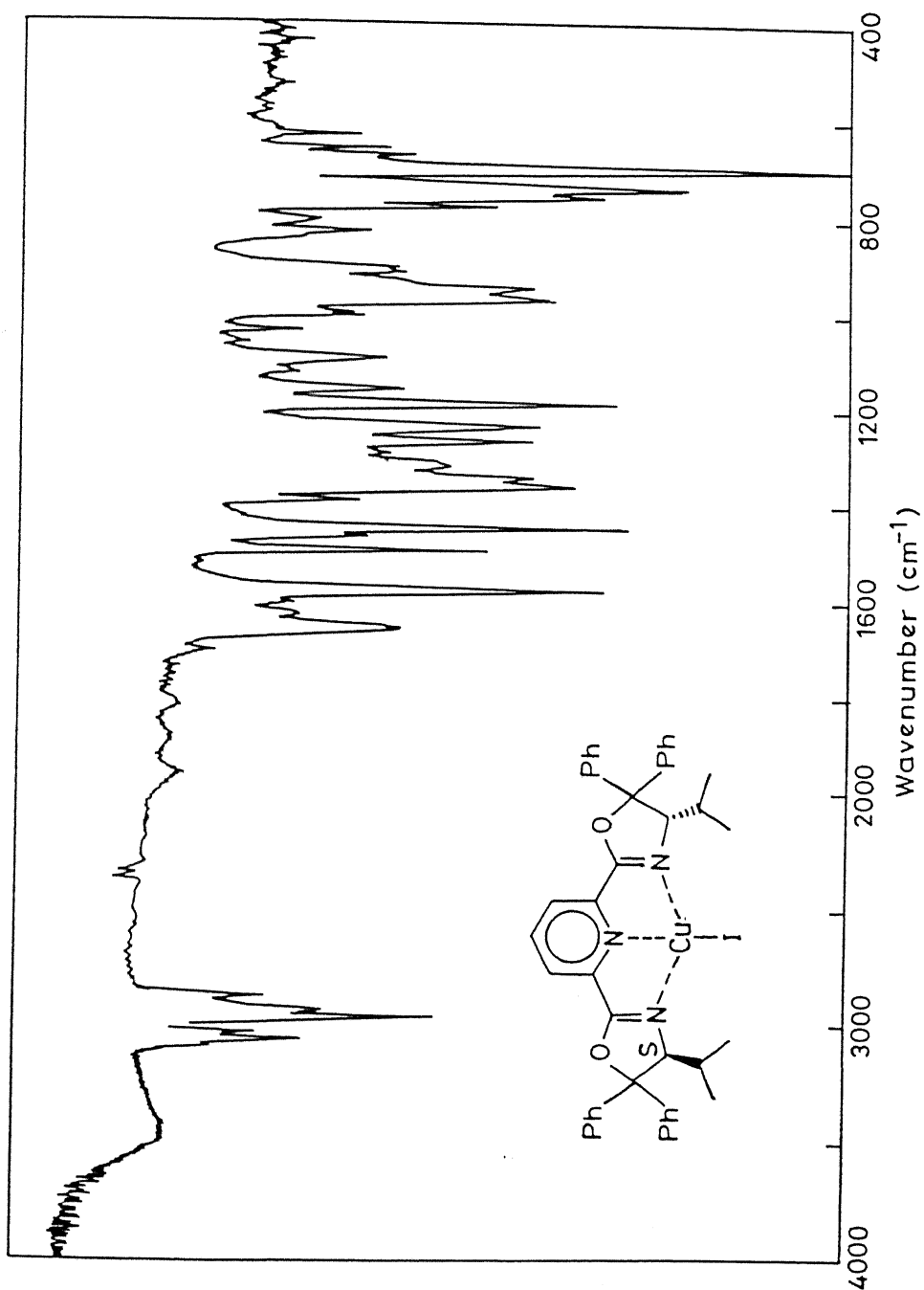
(*S*)-2-Cycloheptenyl-1-benzoate¹⁴ (Table 1; Entry 13): *R*_f 0.61 (2% EtOAc in petroleum ether); IR (neat) 3020, 1700, 1440 cm^{-1} ; ¹H NMR (CDCl_3 , 600 MHz) δ 1.69 (m, 1H), 1.84 (m, 3H), 1.95 (m, 3H), 2.11 (m, 1H), 5.49 (broad singlet, 1H), 5.82 (m, 1H), 5.98 (m, 1H), 7.41 (m, 2H), 7.52 (m, 1H), 8.03 (m, 2H).

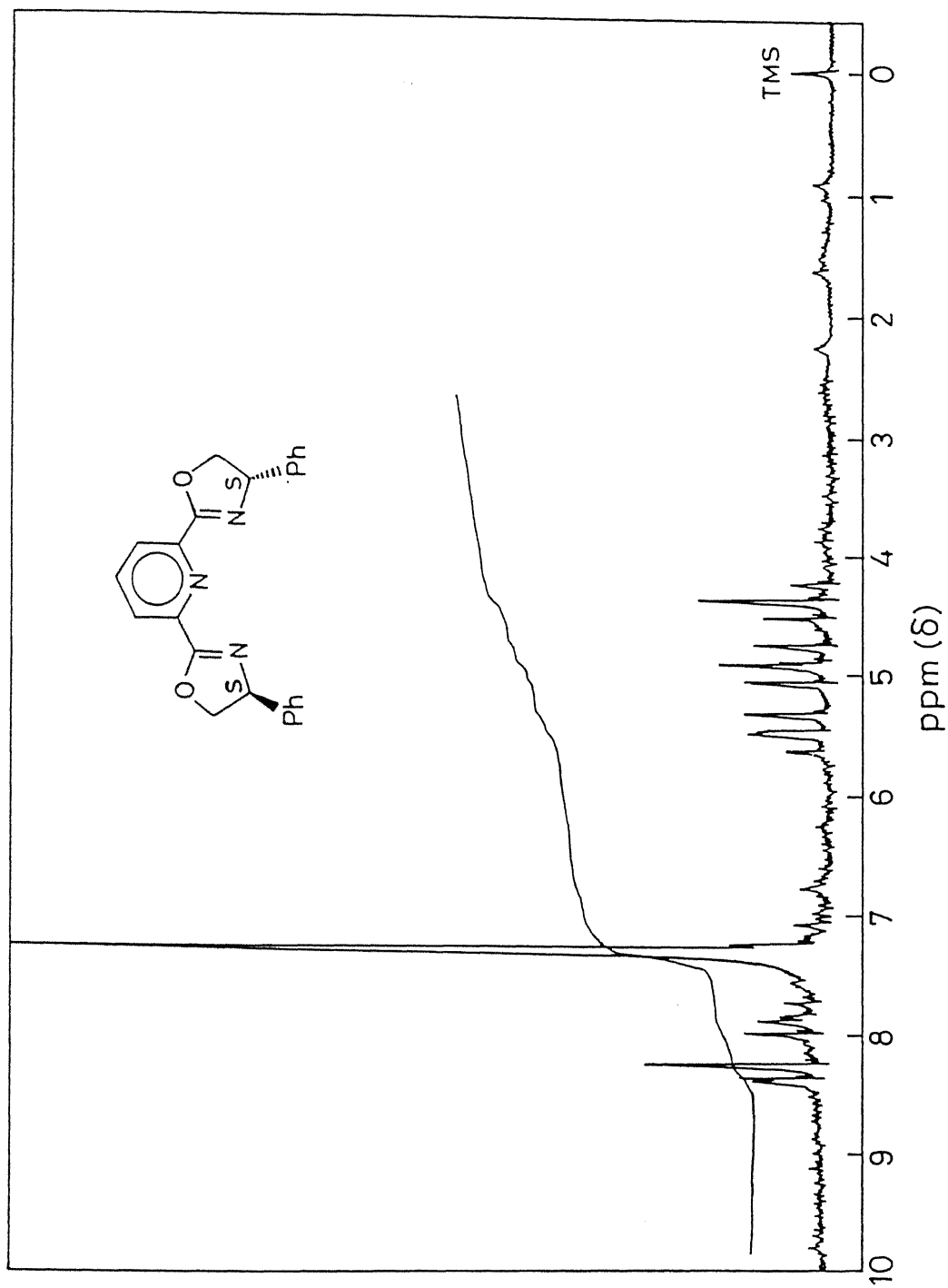
With $\text{Eu}(\text{hfc})_3$, the *ortho* protons of the benzoate shifted and separated in ¹H NMR spectrum (600 MHz). The relative intensities of the two peaks at δ 9.51 ppm (minor) and δ 9.58 ppm (major) gave the enantiomeric excess of 25%. This value matched with the rotation data, $[\alpha]^{25}_{\text{D}} -11.5^{\circ}$ (*c* 2.0, CHCl_3), [lit^{11b} $[\alpha]^{25}_{\text{D}} -10.6^{\circ}$ (CHCl_3) for 23% ee].

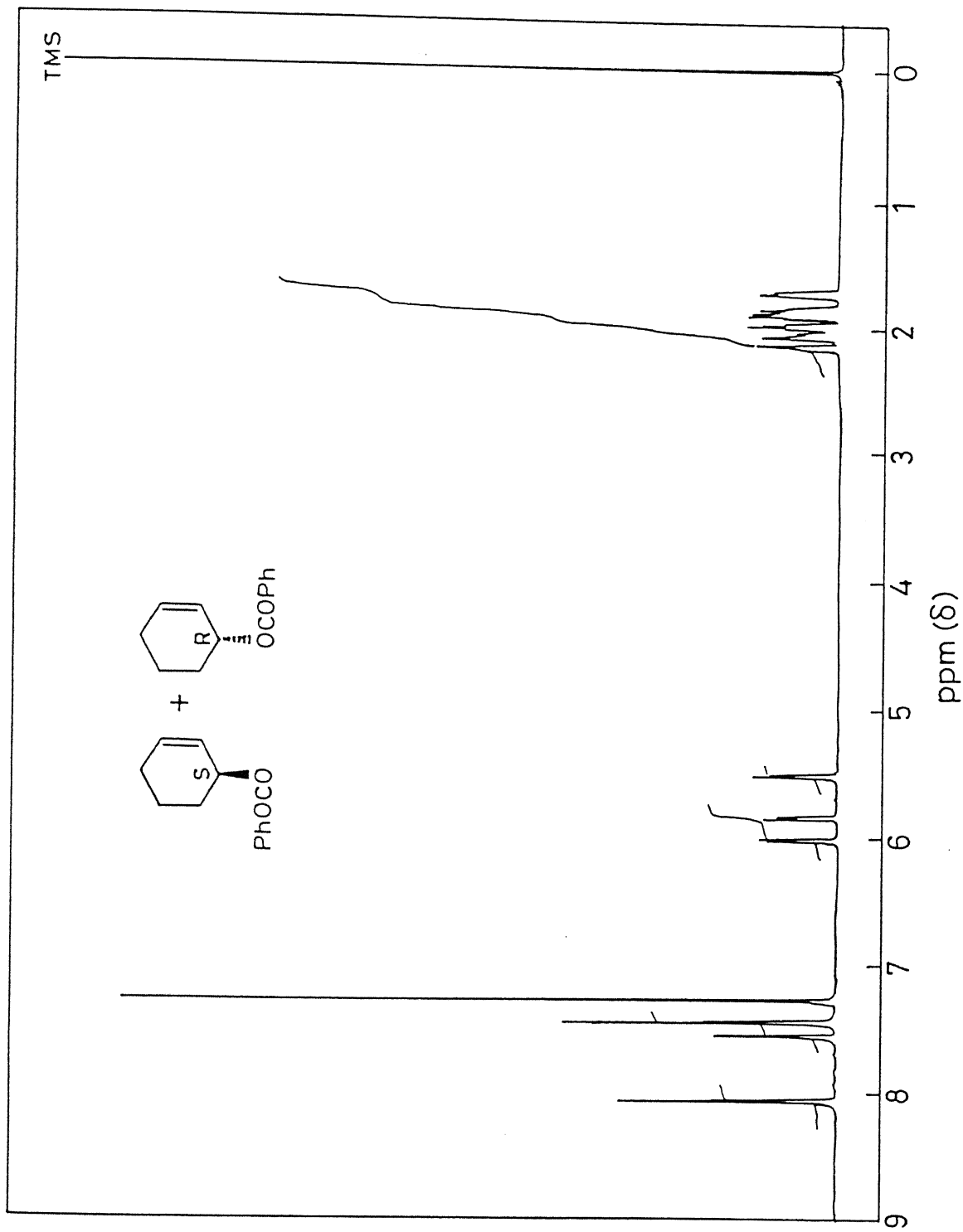




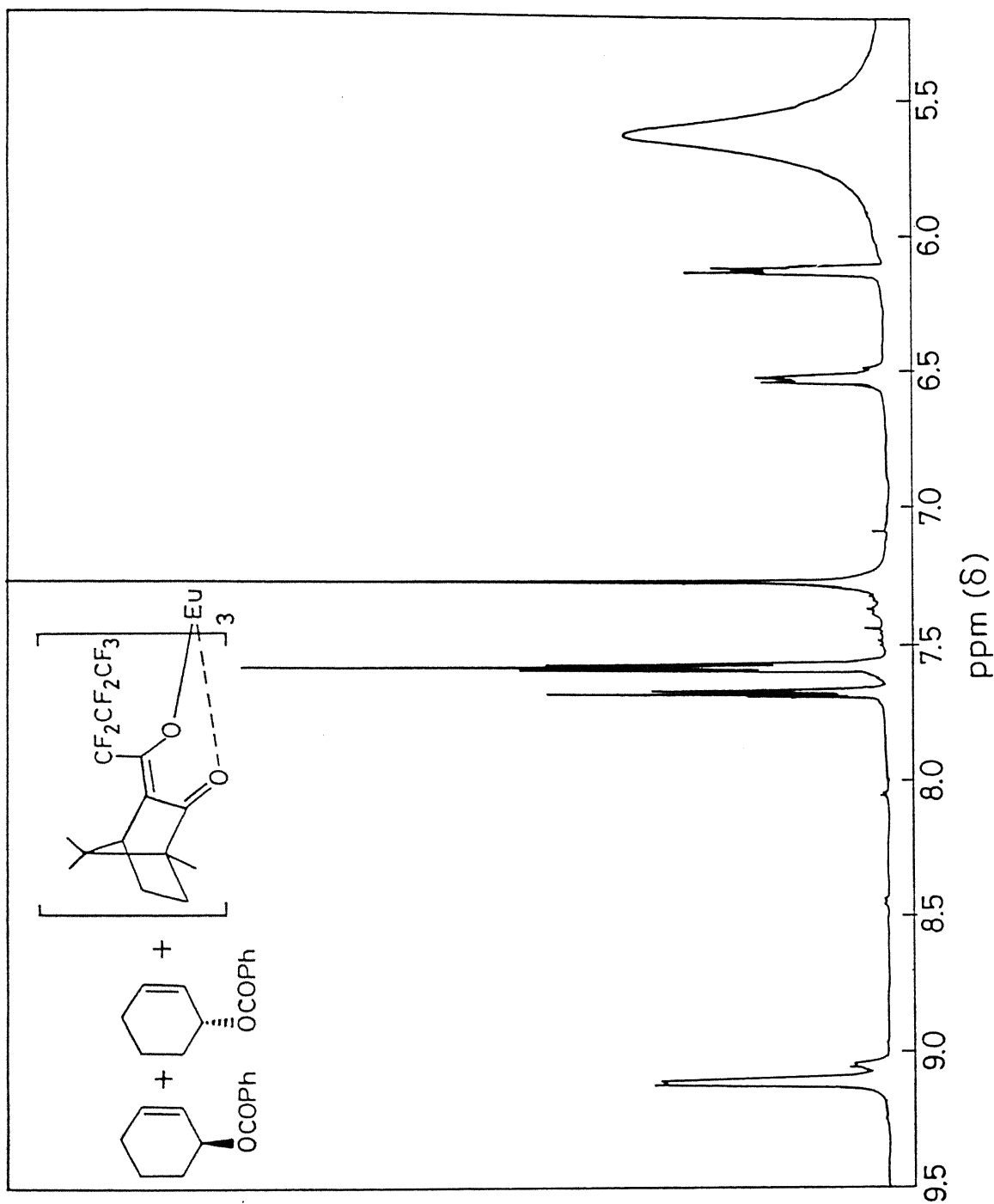
75.469 MHz ^{13}C NMR spectrum of **16** in CDCl_3 .

IR spectrum (KBr) of **16**.

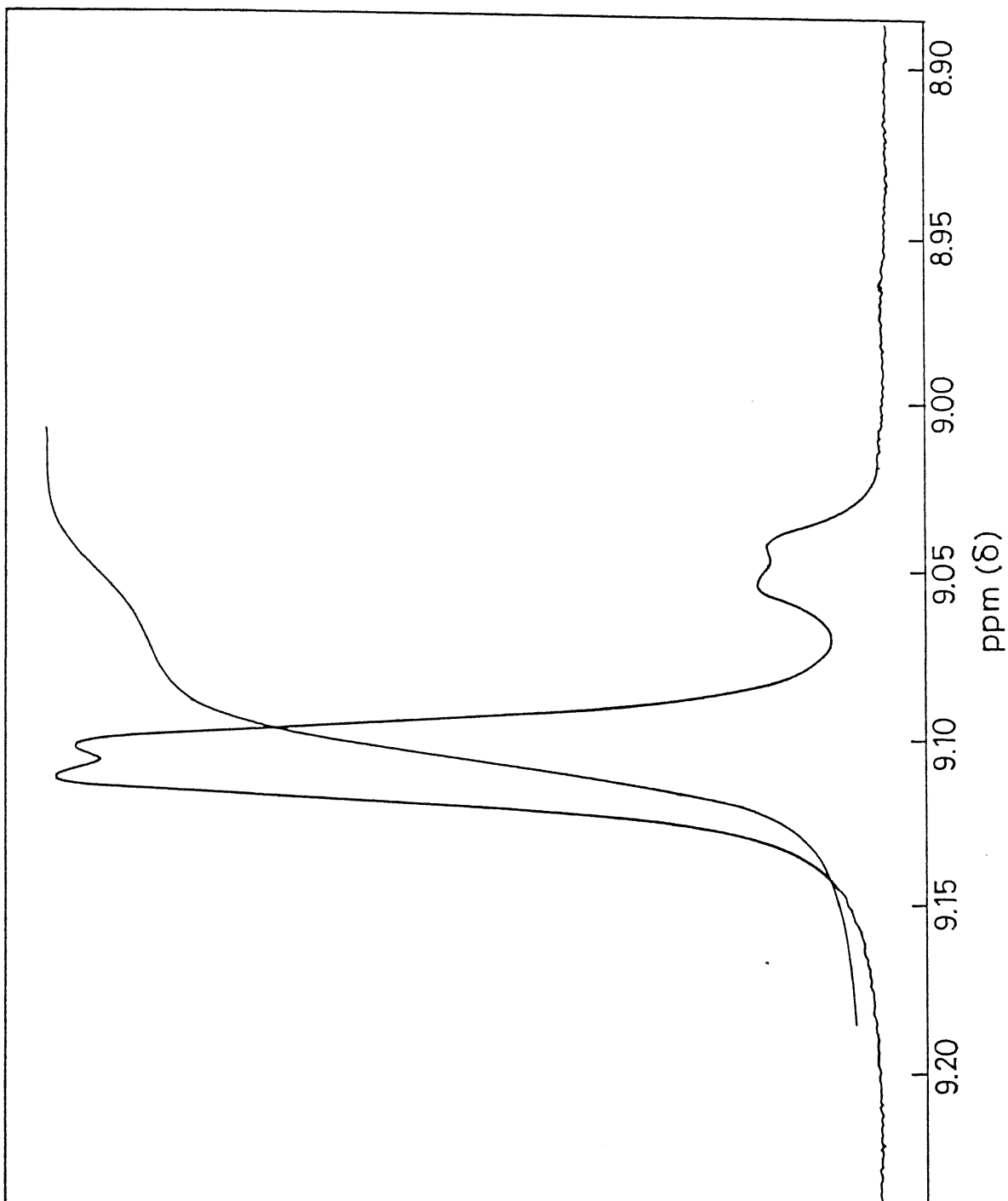
60 MHz ^1H NMR spectrum of **18** in CCl_4 .



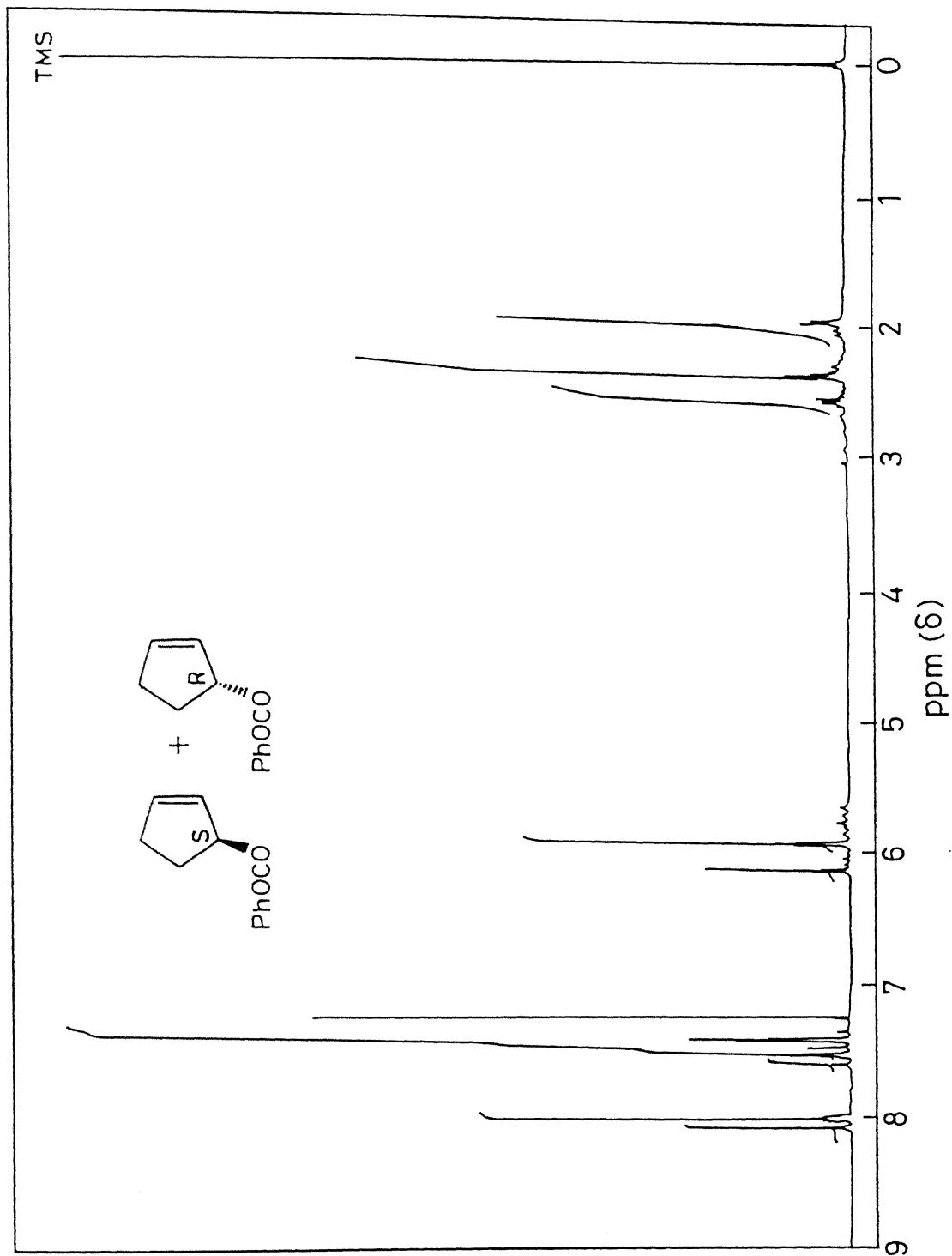
600 MHz ^1H NMR spectrum of 2-Cyclohexenyl-1-benzoate in CDCl_3 .

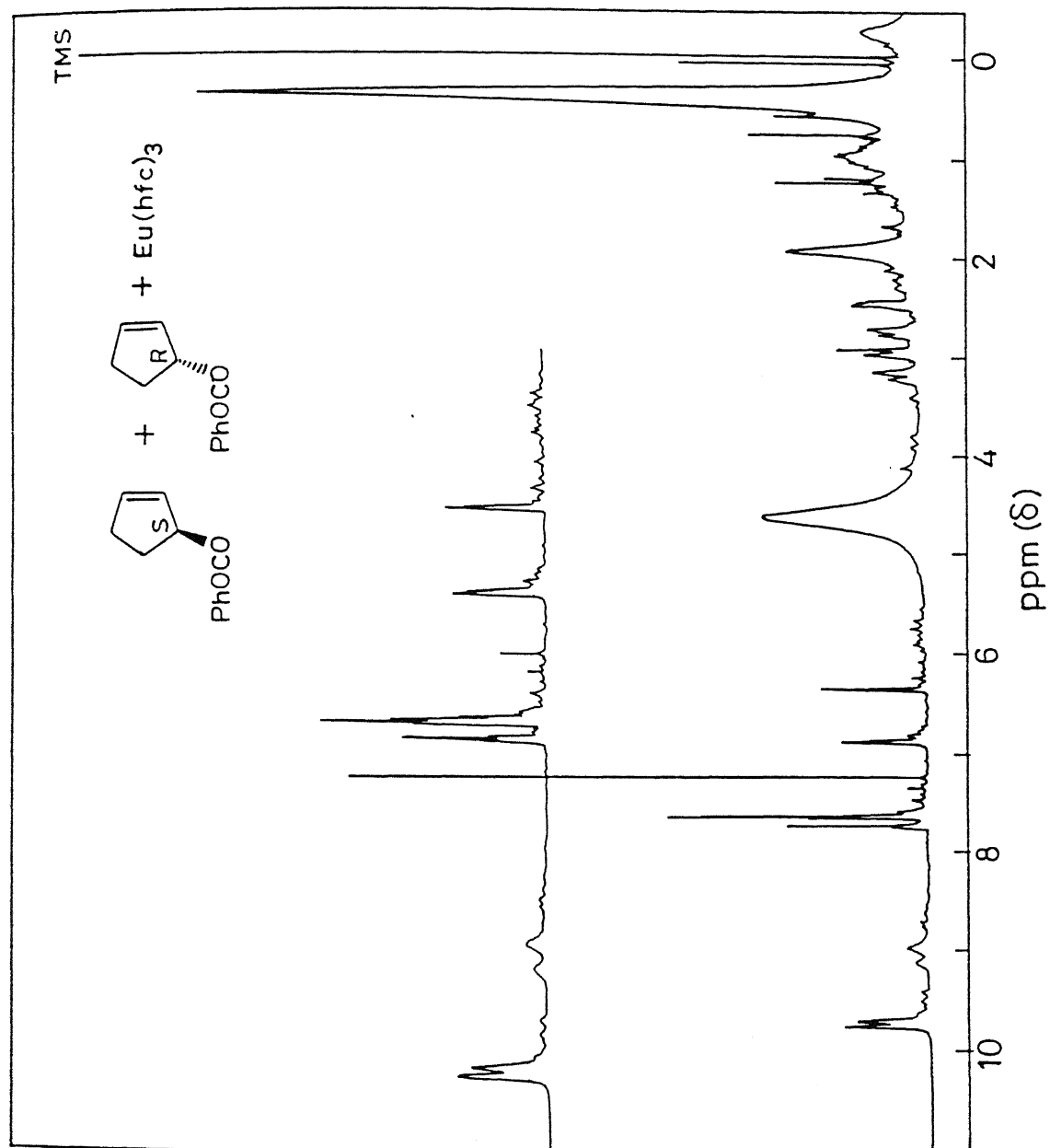


600 MHz ${}^1\text{H}$ NMR spectrum of the shift reagent study of 2-Cyclohexenyl-1-benzoate using $\text{Eu}(\text{hfc})_3$ in CDCl_3 .

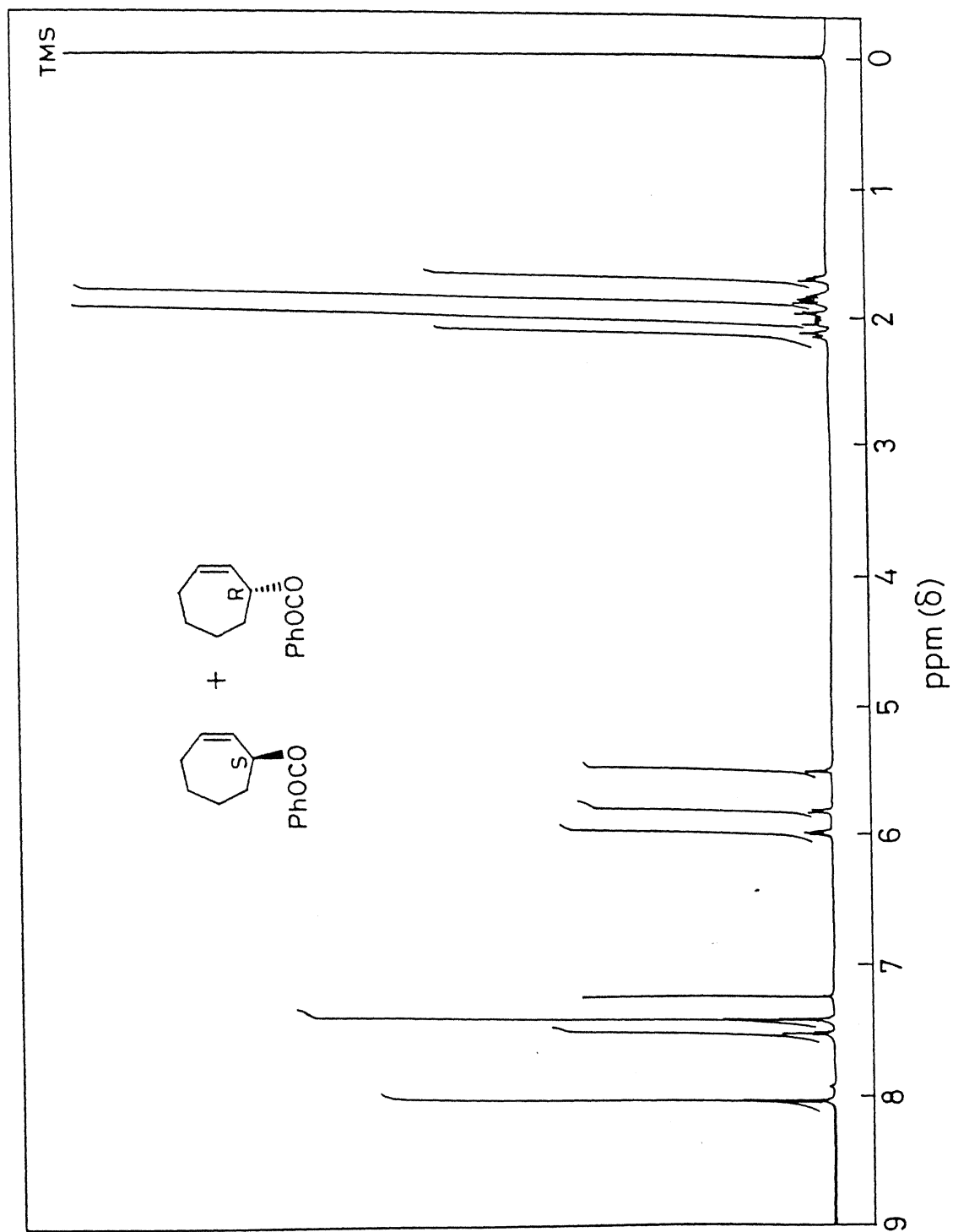


600 MHz ^1H NMR spectrum of the shift reagent study of 2-Cyclohexenyl-1-benzoate using $\text{Eu}(\text{hfc})_3$ in CDCl_3 .

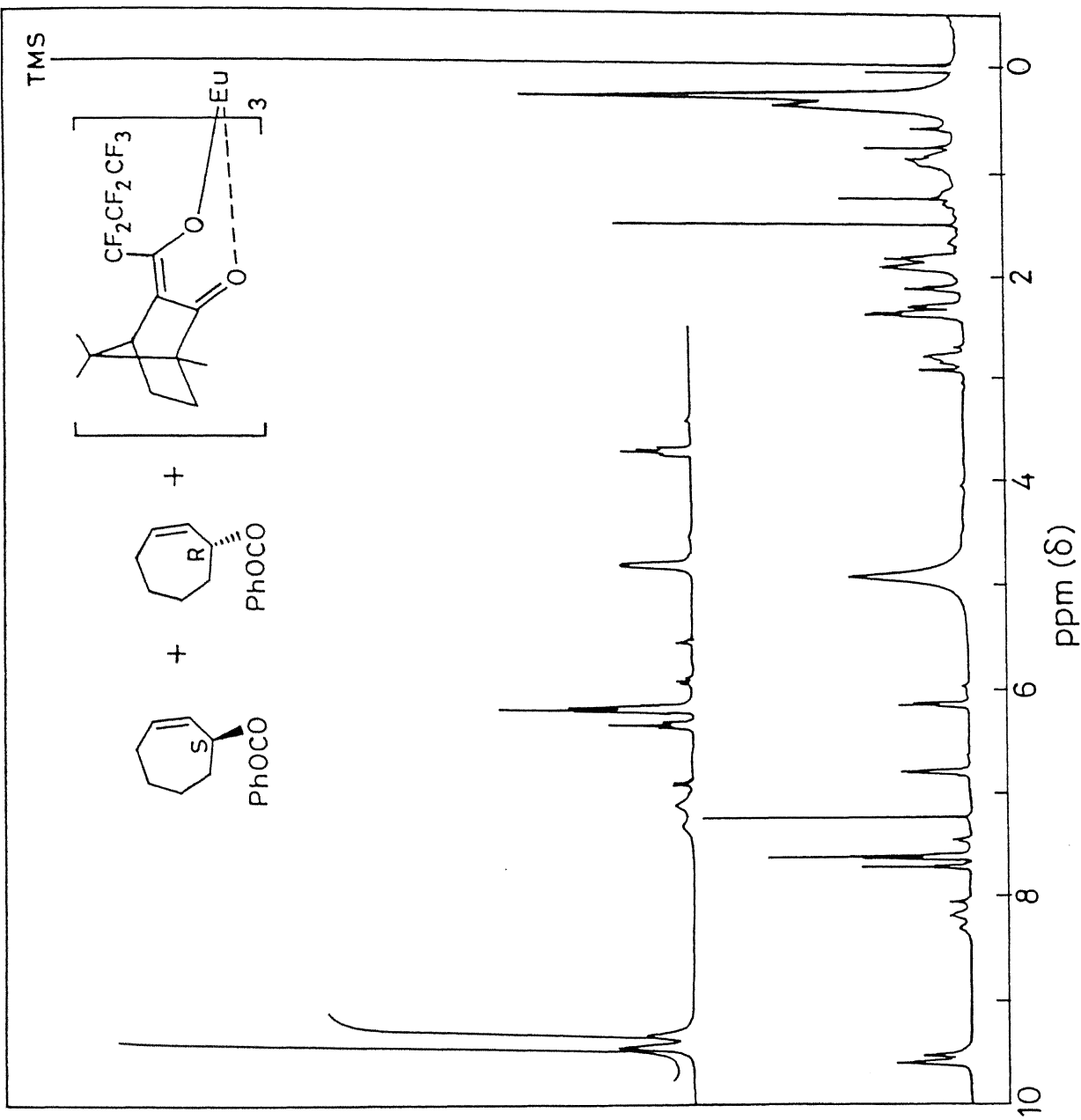
600 MHz ^1H NMR spectrum of 2-Cyclopentenyl-1-benzoate in CDCl_3 .



600 MHz ${}^1\text{H}$ NMR spectrum of the shift reagent study of 2-Cyclopentenyl-1-benzoate using $\text{Eu}(\text{hfc})_3$ in CDCl_3 .



600 MHz ^1H NMR spectrum of 2-Cycloheptenyl-1-benzoate in CDCl_3 .



600 MHz ${}^1\text{H}$ NMR spectrum of the shift reagent study of 2-Cycloheptenyl-1-benzoate using $\text{Eu}(\text{hfc})_3$ in CDCl_3 .

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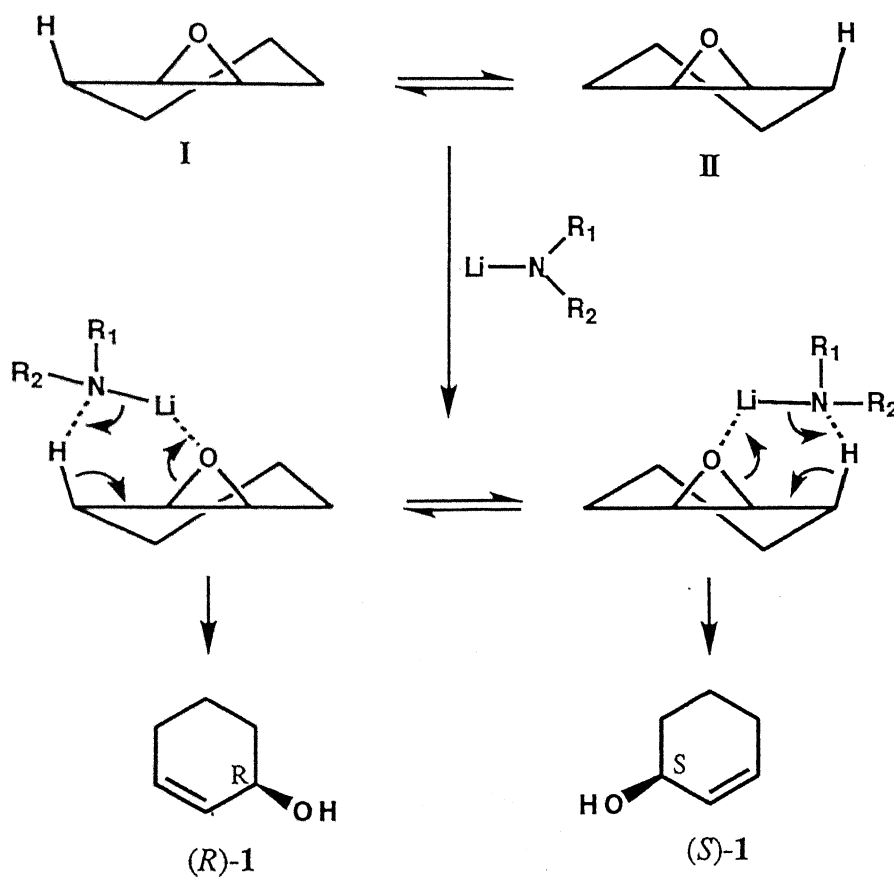
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ENANTIOSELECTIVE DEPROTONATION REACTIONS

Introduction

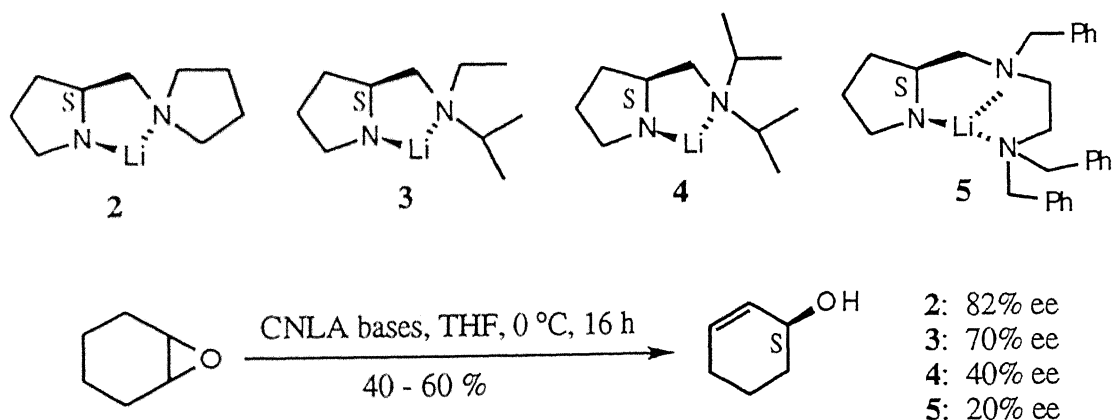
An epoxide usually undergoes three kinds of transformations, viz., nucleophilic ring opening, isomerization under the influence of acidic reagents and isomerization by non-nucleophilic strong bases, such as, lithium amides derived from organic amines. Since in the last category a proton is abstracted by a base, the process is also referred to as deprotonation reaction. Because of the synthetic values of the base-induced rearrangements of epoxides to allylic alcohols, the reaction has been investigated in some detail.¹ In acyclic systems, the reaction proceeds *via* a β -elimination (i.e., 1,2- or E₂-type).^{1a} Cyclohexene oxide has been shown through deuterium-labeling to undergo exclusive *syn* β -elimination in ether.² Complexation of Li⁺ to the epoxide oxygen apparently directs the facial selectivity *via* a six-membered cyclic transition state. The deprotonation here, is highly selective for the proton that occupies the pseudoaxial orientation. Asymmetric version of this reaction can be called as enantioselective deprotonation reaction.



Scheme I

Enantioselective deprotonation of symmetrical epoxides to optically active allylic alcohols using nonenzymatic methods, where enantiotopic proton selection takes place by chiral nonracemic lithium amide (CNLA) bases, is a very challenging area in asymmetric synthesis. Such a kind of conversion of cyclohexene oxide to (*S*)-2-cyclohexen-1-ol **1** was first reported by Whitsell and Felman in a maximum optical induction of 31% ee.^{3,4} They have argued that a chiral base must be able to differentiate the rapidly equilibrating enantiomeric conformations (**I** & **II**) of cyclohexene oxide by forming the diastereomeric transition states (Scheme I). Thus, the structure and chirality of amines will dictate the sense of asymmetric induction in the product.

Later, Asami⁵ and recently, Singh and Bhuniya⁶ from our lab, extended the work further and reported a maximum of 82% ee for the same transformation using (*S*)-proline based base **2**. Singh and Bhuniya⁶ prepared CNLA bases **3** and **4**, and applied them for the deprotonation of cyclohexene oxide. But, unfortunately the **3** gave 70% ee, while 40% ee was obtained with the base **4**. They also synthesized one tridentate ligand to reduce the aggregation around Li, but its chiral lithium amide base **5** gave only 20% ee. In all the cases, (*S*)-CNLA base gave (*S*)-enantiomer of the alcohol **1** (Scheme II).

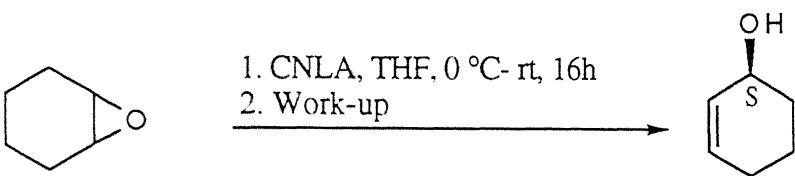


Scheme II

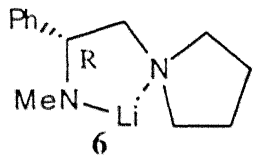
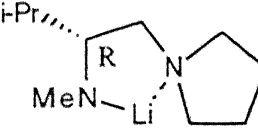
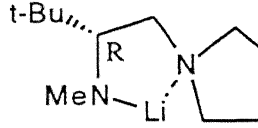
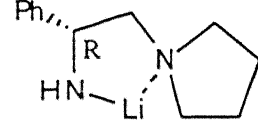
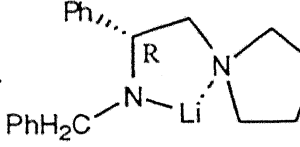
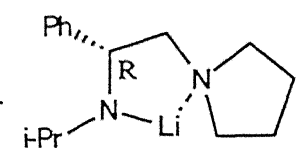
Since (*S*)-proline is easily available for synthesizing (*S*)-allylic alcohols, the methods mentioned above were found to be useful. However, (*R*)-proline being very expensive it is not

economically viable for synthesizing (*R*)-alcohols. Effort has been made towards tuning the (*S*)-proline based ligands in such a way that both the enantiomers of an allylic alcohol can be synthesized, but the enantioselectivity had been moderate⁷. So, Singh *et al.* introduced new kinds of CNLA bases (Table 1),⁸ which can be procured from readily available aminoacids in both the enantiomeric forms.

Table 1:

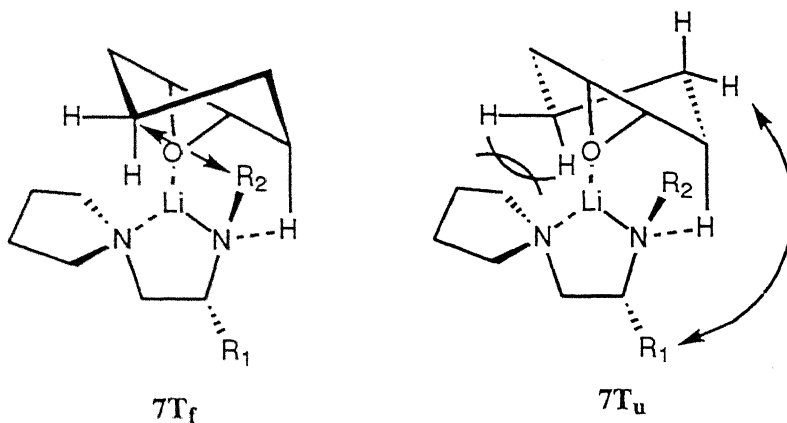


1. CNLA, THF, 0 °C- rt, 16h
2. Work-up

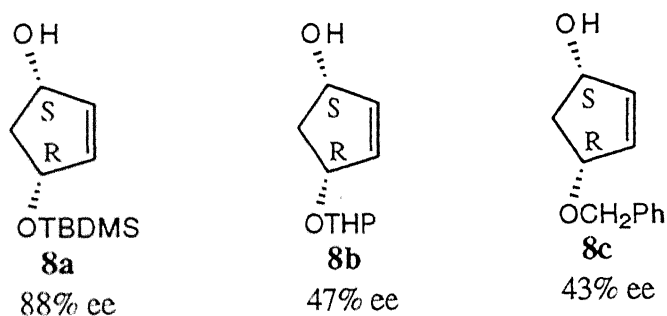
Entry	CNLA	Yield (%)	Config. (% ee)
1.	 <p style="text-align: center;">6</p>	60	S (77)
2.		58	S (60)
3.		55	S (58)
4.		60	RS (00)
5.		52	S (31)
6.		50	S (13)

Among all of them, phenylglycine based base **6** turned out to be the best and it gave 77% ee for the (*S*)-**1** during the deprotonation of cyclohexene oxide. This base was tuned, to some extent,

on a model substrate such as cyclohexene oxide. The high enantioselectivity in the deprotonation of cyclohexene oxide with the base **6** was rationalized by invoking cyclic six-membered transition state model **7T_f** and **7T_u**.



Singh *et al.* further applied the CNLA (*R*)-**6** for the deprotonation reaction of other epoxides.^{8a} The chiral allylic alcohols **8**, which are versatile intermediates⁹ for cyclopentanoid natural products,¹⁰ have been synthesized in our laboratory in a maximum of 88% ee using the base **6**.



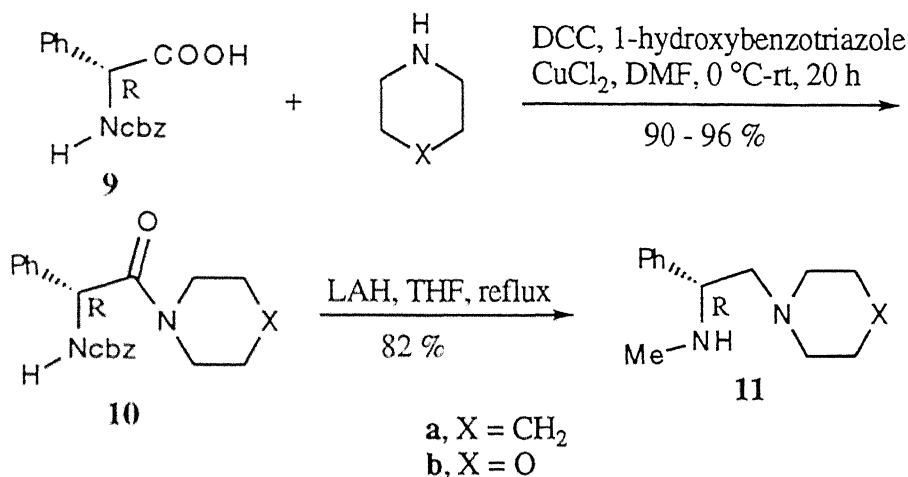
The compounds **8a** had been synthesized in past by others using proline based ligands¹¹ and dilithiated chiral aminoalcohols¹², but, the enantioselectivity remained only upto 86%.

Background

During the last four years, enantioselective deprotonation reaction of symmetrical epoxides has been studied, in great detail, in our laboratory. A number of new chiral ligands have been synthesized, and ultimately a maximum of 77% ee for (*S*)-2-cyclohexen-1-ol was achieved using the phenylglycine based base (*R*)-**6**.^{6,8} The chiral base (*R*)-**6** was also applied by us in synthesizing a series of cyclopentanoid intermediates in a maximum of 88% ee.^{8a} The results were rationalized with a proper transition state model. The most interesting thing was that the diamine ligand could be synthesized in both the enantiomeric forms as (*R*)- and (*S*)- phenylglycine are available at relatively cheap price. With the aim of synthesizing new ligands and applying them for the deprotonation reaction in order to improve the enantioselectivity, we continued the project in our lab.¹³ The main emphasis was to get enantiopure cyclopentanoid intermediate **8a** which is available in only 88% ee. to-date, using chiral base chemistry.

We were also interested to develop a mild and selective method for removal of TBDMS group so that the intermediate could be manipulated into a variety of useful compounds. Our efforts¹⁴ in this direction will be discussed in this chapter as well.

From the introduction section we have seen that cyclohexene oxide has been chosen as a model substrate to tune the CNLA base **6**. Thus, a maximum of 77% ee for (*S*)-2-cyclohexen-1-ol **1** was achieved. In order to see the effect of other cyclic amines in the base **6**, we synthesized two more diamine ligands **11a** and **11b**, in which the pyrrolidine part was replaced by piperidine and morpholine, respectively. These ligands were synthesized from (*R*)-*N*-cbz-phenylglycine (Scheme III).

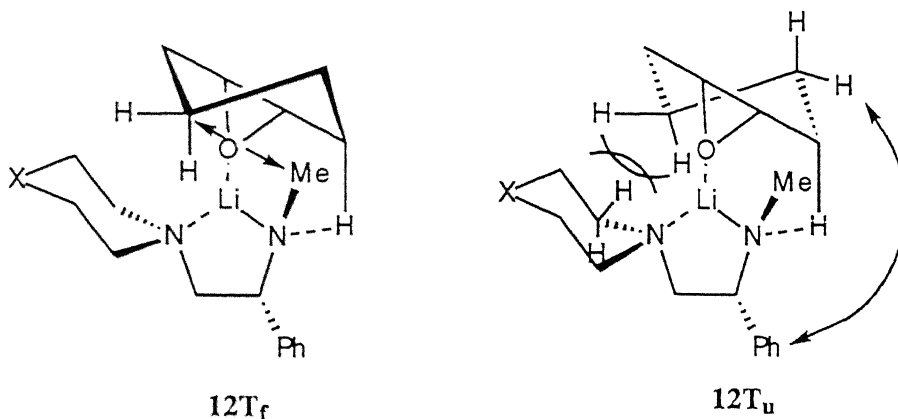


Scheme III

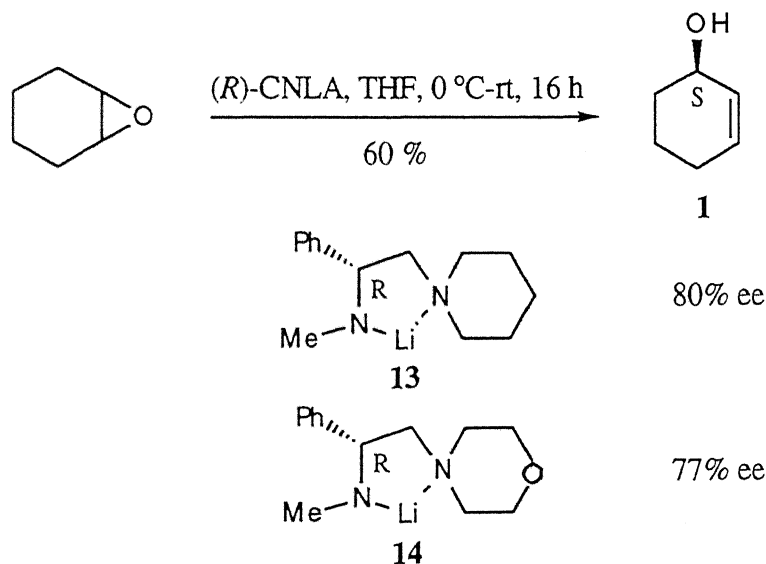
The coupling reaction of *N*-cbz-acids **9** with piperidine/morpholine was carried out with dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxybenzotriazole (HOBT) and cupric chloride.¹⁵ If both the latter reagents were not used, significant amount of racemization took place.¹³ The (*R*)-*N*-cbz-amides **10a** and **10b**, obtained in this way, were reduced to (*R*)-diamines **11a** and **11b** by LAH.

The bases derived from the diamines **11a** and **11b** were used for the deprotonation of cyclohexene oxide. The choice of these amines was based on the close scrutiny of the favoured (**12T_f**) and unfavoured (**12T_u**) transition state models for the reaction. The transition state model **12T_u** is unfavoured due to two very strong non-bonding interactions of epoxide's out-of-plane CH₂s' with phenyl and the cyclic amine's CH₂. The use of piperidine and morpholine, in place of pyrrolidine, was based on our reasoning that because of their larger bond angle, the non-bonded

interaction of its methylene with epoxide's CH₂ will be more, and that will favour the required pathway. However, it was difficult to predict about the chelation effect on enantioselectivity because of change of pKa values of the amines.



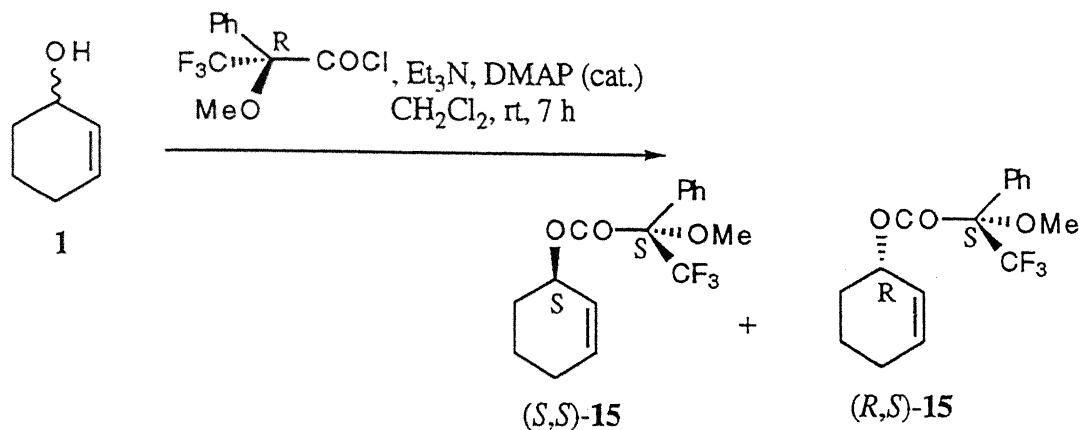
The results of deprotonation of cyclohexene oxide from scheme IV are very close to our prediction. The base **13** derived from the ligand (*R*)-**11a** gave 80% ee whereas the base **14** derived from the ligand (*R*)-**11b** gave 77% ee for (*S*)-2-cyclohexen-1-ol **1**.



Scheme IV

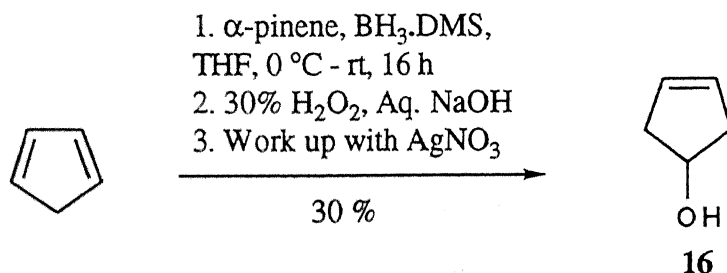
The absolute stereochemistry was assigned based on the sign of the rotation value. The enantiomeric excess was determined by using Mosher's method.¹⁶ We converted the alcohol (*S*)-**1**

into α -methoxy- α -(trifluoromethyl)phenylacetic acid (MTPA) derivative as described for (\pm)-**1** in scheme V. ^1H NMR analysis of the MTPA esters **15** indicated for the alcohol (*S*)-**1** to have a maximum of 80% ee.



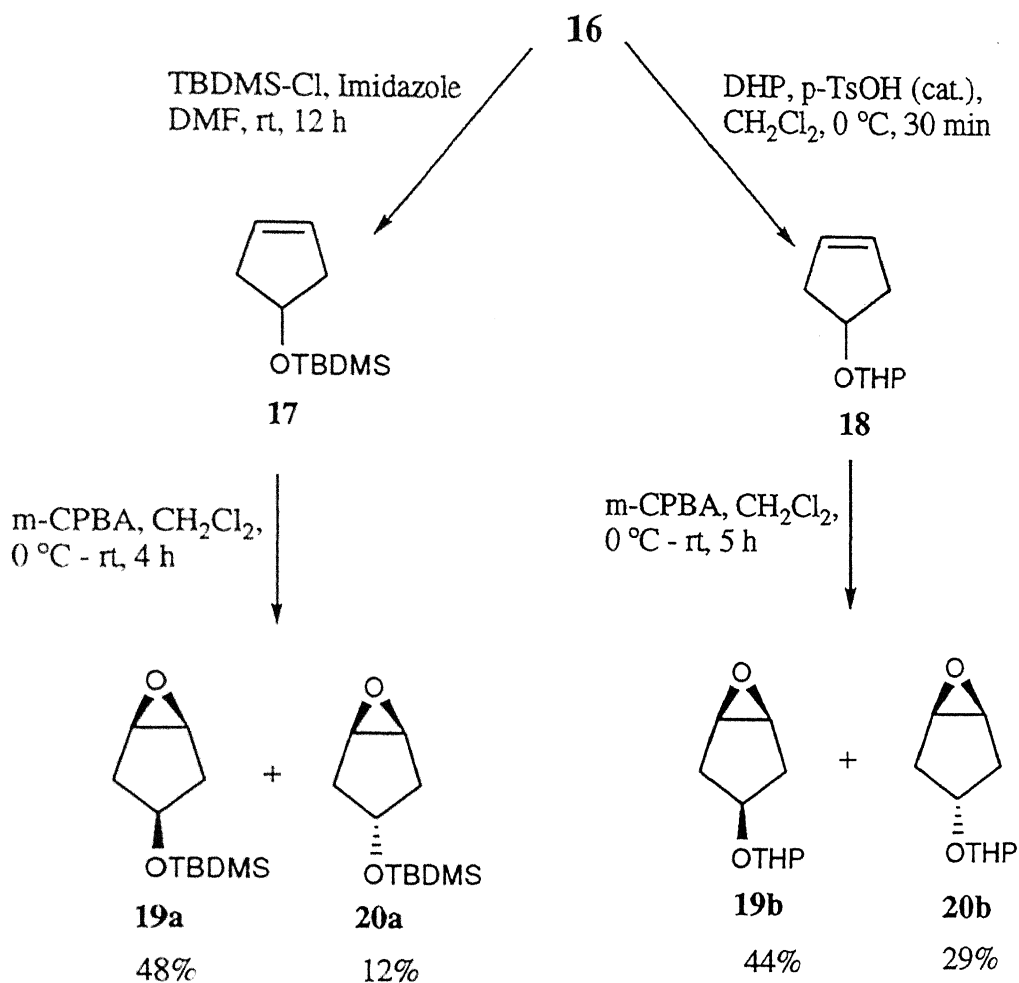
Scheme V

These ligands were then further applied for the deprotonation reactions of the epoxides **19** and **20**. In order to study the deprotonation reaction, *cis*- and *trans*- meso epoxides were synthesized (Scheme VI). Hydroboration of cyclopentadiene followed by oxidative work-up provided 3-cyclopenten-1-ol **16** in 30% yield.¹⁷



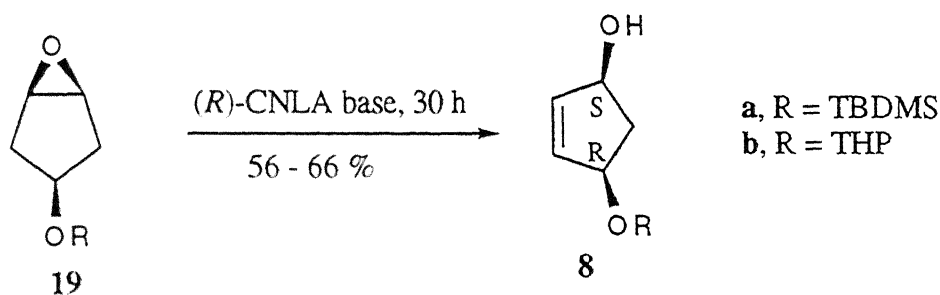
After protecting the hydroxyl group of the **16** with *t*-butyldimethylsilyl chloride (TBDMS-Cl)¹⁸ and dihydropyran, the olefins were epoxidized separately by *m*-CPBA to give a mixture of *cis*- and *trans*-epoxides which were separated by silica gel column chromatography. The *cis*-epoxides were formed in higher ratio compared to the *trans* ones. The ratio of *trans*- and *cis*-isomers indicates that TBDMS ether of **17** has more directing effect for epoxide formation than the tetrahydropyranyl (THP) ether of **18**. This would mean that TBDMS ether shows more chelating

effect than the THP ether. This is in contrast to some reports regarding TBDMS ether as non-chelating group.^{19,20}



Scheme VI

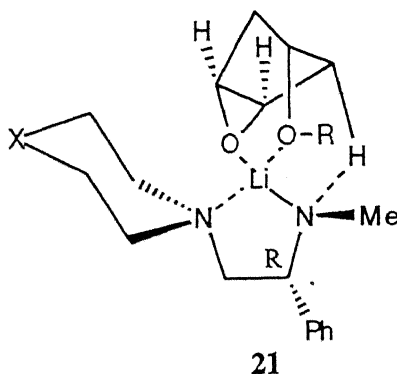
On treatment of *cis*-epoxide **19a** (R=TBDMS) with the CNLA bases (*R*)-**13** and (*R*)-**14**, a very high enantioselectivity was obtained in both the cases. The base (*R*)-**13** gave 97% ee whereas the (*R*)-**14** gave 94% ee in the deprotonation reaction. The enantioselectivity obtained from this reaction is the highest, to-date, for this kind of transformation. Unfortunately, when the same reaction was extended on the *cis*-epoxide **19b** (R=THP) using the base **13**, only 56% ee was obtained. In view of our experience in this area, we tried these deprotonation reactions only in benzene and ether. The isolated yield in all these cases varied from 56 to 66%. The % ees were determined by ¹H NMR measurement of the corresponding Mosher ester. The results are shown in scheme VII.



R	CNLA Base	Solvent	% ee
TBDMS	13	Benzene	97
TBDMS	14	Benzene	94
THP	13	Ether	56

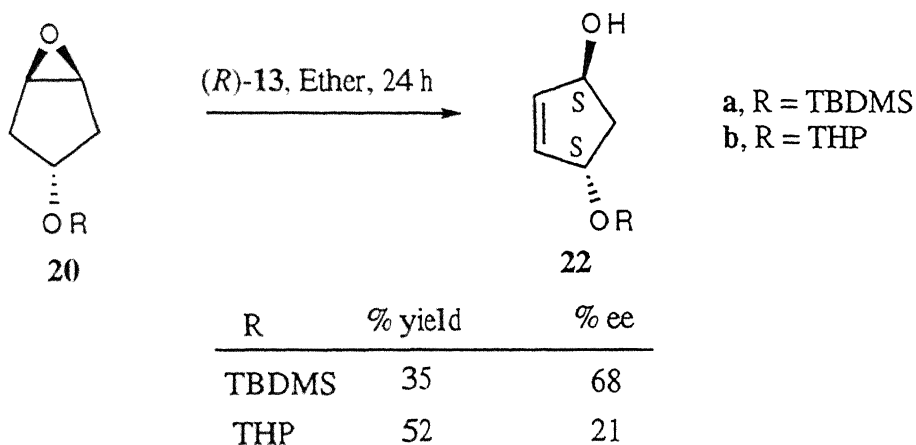
Scheme VII

Such a high level of optical induction in the above reaction indicates that the transition state of the reaction is highly ordered when R is a TBDMS group. The highly chelated transition state model **21** supports the above results. We feel that key to the high asymmetric induction in the reaction is the coordination of ethereal oxygen to the Li metal.



Although, the effect of silicon protecting groups upon the coordinating ability of oxygen had been of much study^{19,20}, we think that in this case the TBDMS ether coordinates Li better than the THP ether during the transition state of the reaction. Partial support for this model also comes from the poor enantioselectivity during the deprotonation of *trans*-epoxides **20** (Scheme VIII). This could be due to absence of strong chelation by ethereal oxygen because of its *trans* orientation.

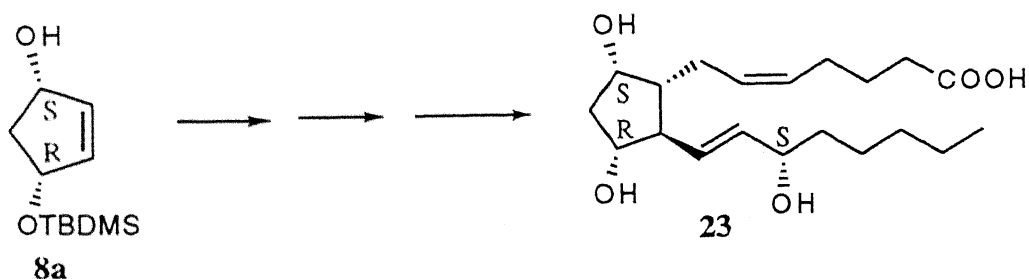
Chelating effect of TBDMS ether was also seen during the formation of *cis*-epoxide **19a** (*vide supra*).



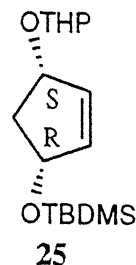
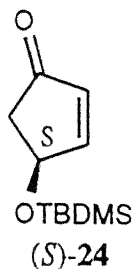
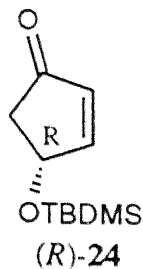
Scheme VIII

The absolute stereochemistry of the products was determined by comparing the rotation data with the literature.^{11d} In all the cases the enantiomeric excesses were determined by 400 MHz ¹H NMR analysis of the corresponding Mosher ester.

Conversion of the allylic alcohol (1*S*,4*R*)-**8a** to prostaglandin **23** is well established in the literature¹⁰, so the synthesis of **8a** in 97% ee is an important contribution to this area.



The above transformation has been done *via* intermediate (*R*)-**24**. One can synthesize its enantiomer (*S*)-**24** from *ent*-**8a** which can be obtained *via* deprotonation chemistry using the *S*-enantiomer of the chiral base. In literature^{11d}, the intermediate (*S*)-**24** has been synthesized from **8a** *via* **25** using the chemoselective deprotonation of TBDMS group with fluoride ion. While studying the chemoselective deprotection of TBDMS/THP ether **25**, we were able to develop a mild and new method for the cleavage of *tert*-butyldimethylsilyl and tetrahydropyranyl ethers.

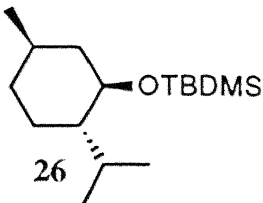
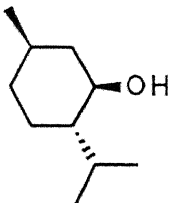
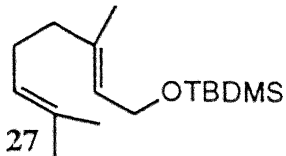
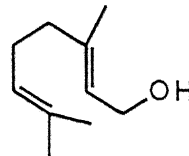
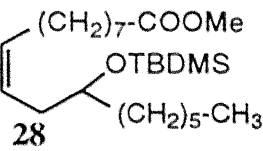
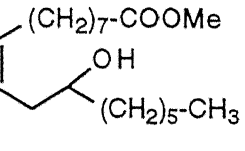
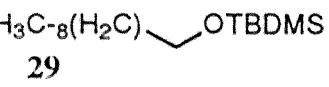
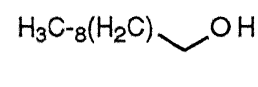
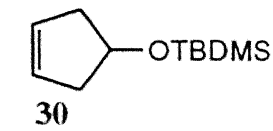
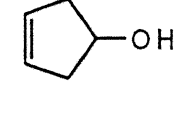
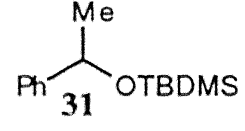
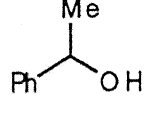

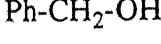


Success of any protective group largely depends upon its stability to acidic or non-acidic reagents, and how easily it can be installed and deprotected. Protection of alcohol as tert-butyldimethylsilyl (TBDMS)¹⁸ ether is very well utilised in organic synthesis because of its easy installation^{18,21} and general stability to basic and mild acidic reagents.¹⁸ The deprotection of TBDMS ethers is usually done with aqueous acids,^{18,22} fluoride ion,¹⁸ and aqueous HF-CH₃CN.²³ Since strong acidity of aqueous acids is undesirable for acid sensitive substrates, a less acidic reagent, fluorosilicic acid was introduced few years ago.²⁴ Although tetrabutylammonium fluoride^{18,25} is the most popular for deprotection of TBDMS ethers, fluoride ion in aprotic solvent, being a strong base, can affect base sensitive substrates.²⁶ There are several other methods for the cleavage of TBDMS ethers, such as catalytic transfer hydrogenation using Pd,²⁷ Lewis acids in acetonitrile,²⁸ pyridinium p-toluenesulphonate (PPTS),²⁹ etc.³⁰ Recently Corey³¹ published reductive cleavage of TBDMS ethers by DIBAL-H. Although the method is mild, it can not be used in the presence of other reducible functional groups. Some more desilylating reagents such as SiF₄³² and DDQ³³ were recently introduced in the literature. We report herein a mild method for the cleavage of TBDMS ethers under mild conditions using ceric ammonium nitrate (CAN) in methanol. We further report that THP ethers can also be deprotected with CAN in methanol.³⁴

CAN has been used in a variety of oxidative free radical reactions³⁵, but, to the best of our knowledge, it has not been used in the cleavage of TBDMS ethers. Survey of the literature³⁶ suggested that under the conditions (acetonitrile:water, 0 °C) for removal of p-methoxyphenyl and p-methoxybenzyl groups by ·CAN, TBDMS and other silicon groups remain untouched.³⁷ We noticed that CAN in methanol deprotects TBDMS ethers in an efficient manner. We synthesized a variety of TBDMS ethers with different steric and electronic environment. In general, the alcohols were converted to the TBDMS-ethers following the literature procedure,¹⁸ using TBDMS-Cl and

imidazole in DMF. We studied the cleavage of the TBDMS ethers in various solvents. It was observed that reactions were clean only in methanol and the results have been summarized in table 2.

Table 2. Deprotection of tert-Butyldimethylsilyl Ethers by CAN in MeOH at 0 °C.^a

Entry	Substrate	Product	Time	% Yield ^b
1.			2.5 h	95
2.			15 min ^c	97
3.			2.5 h ^d	95
4.			15 min	98
5.			30 min ^c	92
6.			1.5 h	86
7.			30 min	82

^a Stoichiometric amount of CAN was used in the reaction. ^b Isolated yields. ^c Catalytic amount (10 mole %) of CAN also gave quantitative yield of the product but the reaction time was 1.5 h.

^d With 10 mole% of CAN, reaction was very slow and more than 8 h was required for completion of the reaction.

It was further observed that in case of primary and allylic substrates (entries 2 and 4), the reaction was complete within 15 min but the hindered substrates (entries 1 and 3) required 2-3 h. Benzylic TBDMS ethers could also be cleaved in high yield (entries 6 & 7). The deprotection of TBDMS ethers was catalytic in nature but the reaction time, required for completion of the reaction,

was more as it was observed that reactive TBDMS ethers (entries 2 & 5) required 1.5 h for completion of the reaction if 10 mole% CAN was used. However, hindered substrates required a much longer time if catalytic amount of CAN was used in the reaction (entry 3). Thus, it is advisable to use stoichiometric amount of CAN for the deprotection reactions. Since the reaction in methanol was smooth, other solvents were not optimized. Preliminary investigation indicated that the combination of acetonitrile and methanol (19 : 1) was equally good for the same purpose. However, the combination of acetonitrile and water or acetonitrile alone was not found suitable for the reaction. For example, the TBDMS ether **29** of decanol, on reaction with CAN in acetonitrile at 0 °C for 30 min, gave required product in 35% yield and 30% unreacted material was recovered. The same reaction, when run in acetonitrile - water (20:1) under the same conditions, gave 70% alcohol as a required product and 15% unreacted material. Comparison of these results with that of entry 4 in the table 2 suggested that methanol was a superior solvent as the reaction was complete in 15 min and the yield was quantitative.

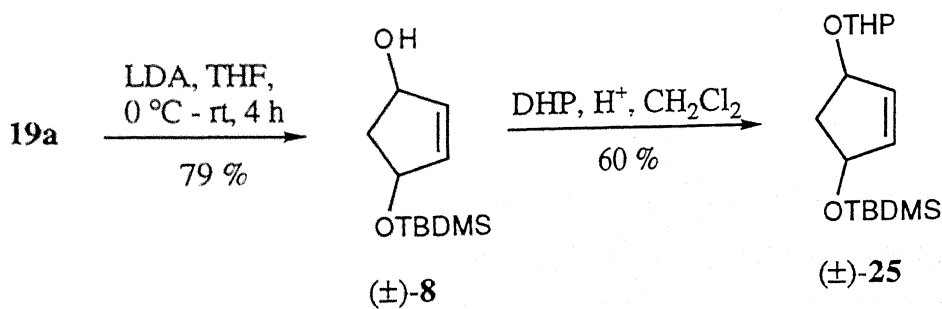
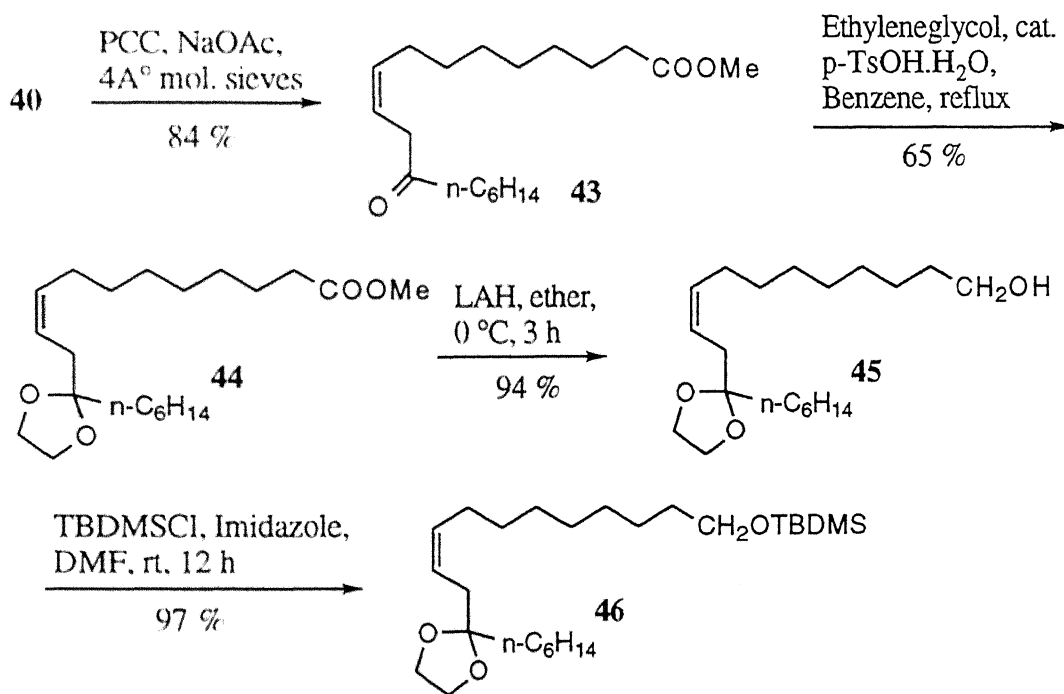
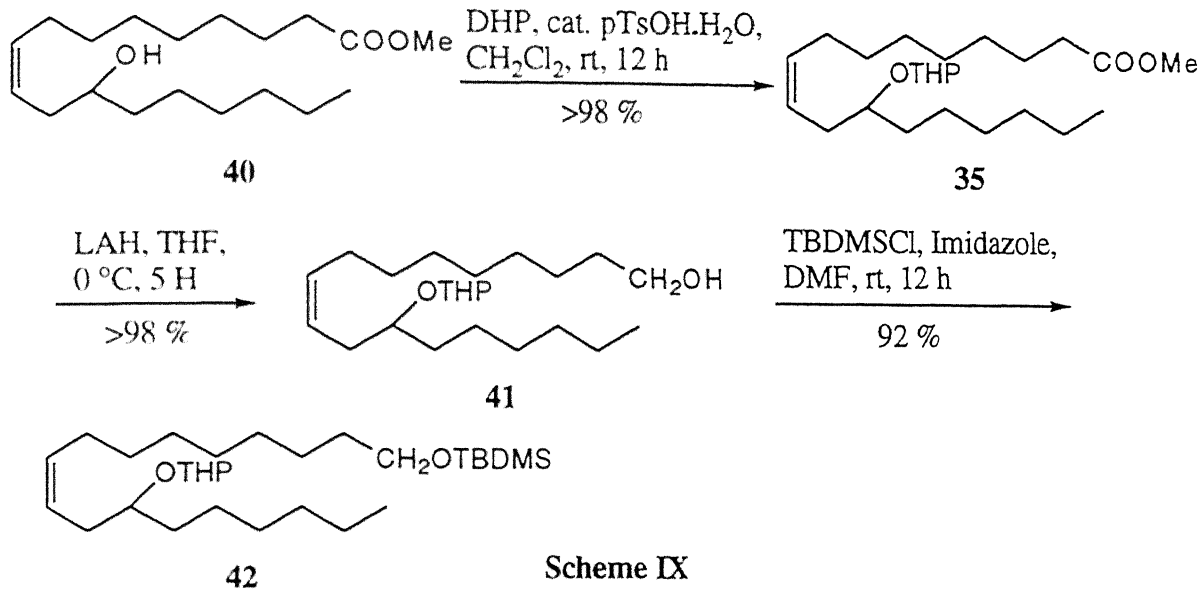
We studied CAN induced deprotection of THP ethers. The THP ethers, in general, were prepared from the corresponding alcohols, using 3,4-dihydro-2H-pyran and a catalytic amount of p-TsOH.H₂O in CH₂Cl₂. We noted that the THP ethers were also successfully cleaved with CAN in methanol at 0 °C. The results are summarized in table 3. In all the cases, the yields were quantitative. It was found that barring menthyl THP ether **33** (entry 1), other THP ethers required 2-3 h at 0 °C for completion of the reaction. It was noted that the temperature lower than 0 °C made the reaction sluggish. The cleavage of THP ethers was studied in a variety of solvents, viz., MeOH, CH₃CN:MeOH (19:1), CH₃CN:H₂O (19:1), benzene:MeOH (2:1). The reaction was clean only in methanol and other solvents gave poor results. The acetonitrile-methanol combination worked equally well. However, acetonitrile-water and benzene-methanol combinations gave poor results. For example, the THP ether of decanol **36**, on reaction with CAN in acetonitrile - water (20:1) or in acetonitrile alone for 3 h at 0 °C gave less than 20% alcohol as a deprotected product. Solvents such as ethanol, isopropanol, and *tert*-butanol gave poor results.

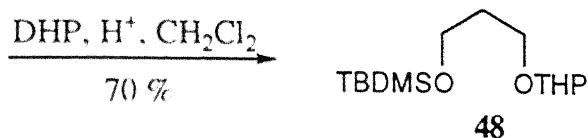
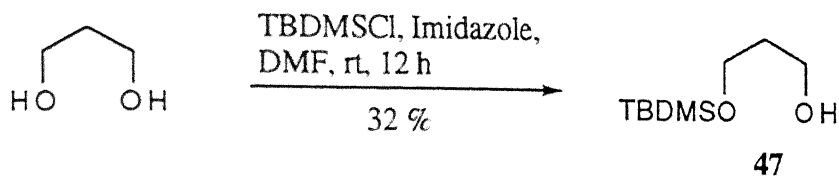
Table 3. Deprotection of THP Ethers by CAN in MeOH at 0 °C.^a

Entry	Substrate	Product	Time	% Yield ^b
1.			30 min	90
2.			3 h	80
3.			2.5 h	91
4.	$\text{H}_3\text{C}-8(\text{H}_2\text{C})-\text{CH}_2\text{OTHP}$ 36	$\text{H}_3\text{C}-8(\text{H}_2\text{C})-\text{CH}_2\text{OH}$	3 h	98
5.			1.5 h	95
6.			3 h	81
7.	$\text{Ph}-\text{CH}_2-\text{OTHP}$ 39	$\text{Ph}-\text{CH}_2-\text{OH}$	3 h	89

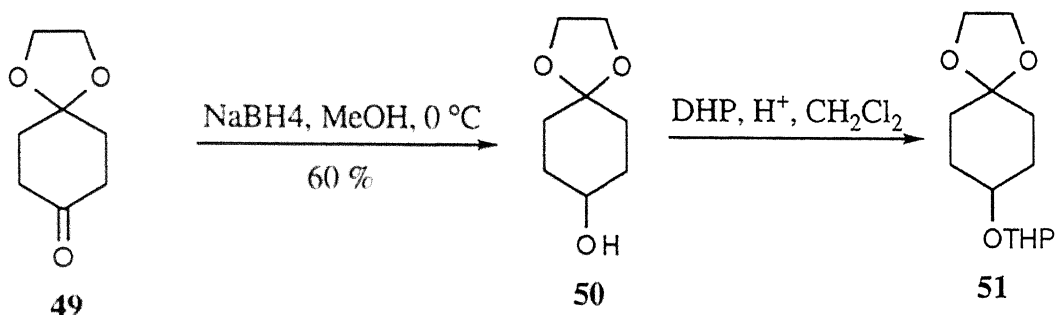
^aStoichiometric amount of CAN is required for completion of the reaction.^bIsolated yields.

After the above studies, we extended the deprotection reaction for chemoselective cleavage of TBDMS/THP ethers and other protecting groups. A variety of substrates were synthesized as per the scheme IX to XIV. These substrates were then subjected to CAN in MeOH. The usefulness of the reaction was seen in the selective cleavage of primary TBDMS ether over secondary THP ether in the case of **42** (Table 4; entry 1) on use of 1.2 equivalent of the reagent. On the other hand, both the groups got cleaved with 2.2 equivalent of the CAN in methanol (Table 4; entry 2).

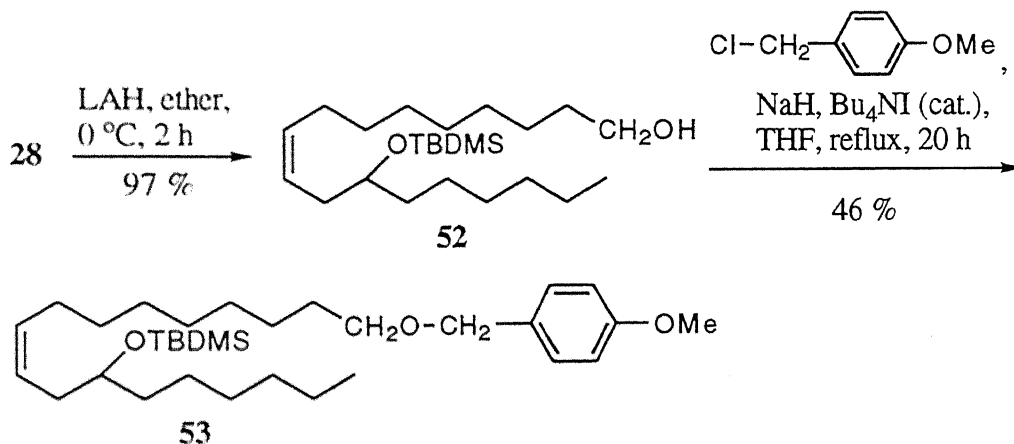




Scheme XII



Scheme XIII

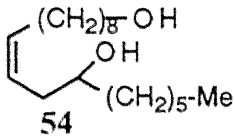
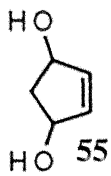



Scheme XIV

It was also found that primary TBDMS ether could be selectively cleaved in the presence of a ketal group in the substrate **46** (Table 4; entry 3). We turned our attention to the cyclopentanoid intermediate (\pm)-**25**. Unfortunately, we found that the selective cleavage of TBDMS or THP ether in (\pm)-**25** with CAN did not take place, albeit both the groups got cleaved within 30 min (Table 4; entry 4). The similar kind of results was obtained in case of **48** where there was no selectivity (Table 4; entry 5). In **51**, the THP ether got selectively cleaved in the presence of ketal group

(Table 4; entry 6). The substrate **53** is unique in the sense that it has both the p-methoxybenzyl group and TBDMS group. Its reaction with 2.2 equivalent of CAN in methanol at 0 °C cleaved both the groups in 90 min (Table 4; entry 7). Controlled study with 1.2 equivalent of the reagent showed a little faster rate of cleavage of p-methoxybenzyl group compared to the *tert*-butyldimethylsilyl group.

Table 4. Chemoselective Deprotection by CAN in MeOH at 0 °C.

Entry	Substrate	Product	CAN (equiv.)	Time	% Yield
1.	42	41	1.2	15 min	95
2.	42	 54	2.2	90 min	96
3.	46	45	1.2	30 min	82 ^a
4.	(±)- 25	 55	1.2	30 min	90
5.	48		1.2	30 min	90
6.	51	50	1.2	90 min	90 ^a
7.	53	54	2.2	90 min	88

^aDuring the reaction period the ketal is hydrolysed to a extent of 5-10%.

The mechanism of the reaction is not very clear to us. Since CAN is a good electron acceptor (reduction potential 1.61 V), probability of electron transfer mechanism is there. But, as it is observed that in some cases the reaction is complete with less than one equivalent of CAN, electron transfer mechanism is less likely to happen.³⁸ The acid catalyzed cleavage can not be ruled out as the pH of the medium is around 4 (pH paper) during the reaction period.³⁹ We assume that an activated complex⁴⁰ of MeOH and CAN is responsible for the above deprotection reactions. It is known in the literature that Ce(IV) forms 1:1 red-coloured complex with alcohols.⁴¹ Oxidation

of methanol with CAN is well known but it is extremely slower than the deprotection of TBDMS and THP ethers. Since methanol is in large excess (as a solvent), its oxidation becomes negligible under the deprotection conditions.^{41a} It is assumed that the attack of methanol of the activated complex on the silicon group is facilitated by coordination of Ce(IV) with the oxygen. The poor results in other alcoholic solvents could be due to its poor complexation with CAN which results in poor nucleophilicity.

Conclusion

In conclusion we have prepared new kind of chiral nonracemic lithium amide bases for deprotonation reactions of various epoxides. We have achieved a maximum of 80% ee in the conversion of cyclohexene oxide to 2-cyclohexen-1-ol. We have also synthesized an enantiopure core unit in 97% ee which is very useful for prostaglandin synthesis. The latter enantioselectivity is the highest, to-date, for this kind of transformation. We have shown that the TBDMS and THP ethers are cleaved with CAN under very mild conditions. The present method will have wide scope in view of the high usefulness⁴² of the TBDMS group in organic synthesis. The significant feature of the reaction is that the cleavage of TBDMS ethers is catalytic in nature. The selective cleavage of TBDMS ether in the presence of THP ether and ketal group is of paramount importance, though the selectivity was found to be substrate specific.

General considerations

The common materials and methods have been given in the experimental section of Chapter-1. (*S*)- α -methoxy- α -(trifluoromethyl)phenylacetic (MTPA) acid (98% ee) was purchased from Aldrich. Corresponding MTPA-Cl was made following a literature method.^{16b} The *n*-BuLi in hexane (1.74 M) was obtained from E-Merck and was titrated by 2-butanol using 1,10-phenanthroline (Aldrich sample) as indicator.⁴³ 1-Phenyl ethanol was prepared from acetophenone by reduction with NaBH₄ in MeOH. Methyl ricinoleate was obtained from castor oil, on reaction with Na in MeOH. Cyclopent-3-en-1-ol was prepared according to the literature procedure¹⁷ (*vide infra*). 4-Oxo-cyclohexanone ethylenediolketal **49** was available in our lab. N,N'-dicyclohexylcarbodiimide, 1-decanol and dicyclopentadiene were purchased from E-Merck. (*R*)-Phenylglycine, carbobenzyloxy chloride (50% in toluene), cyclohexene oxide, 1-hydroxybenzotriazole, anhydrous CuCl₂, borane-DMS solution, 3,4-dihydro-2H-pyran, *m*-chloroperbenzoic acid (50%), imidazole, morpholine, α -pinene, geraniol, (-) menthol, sodium hydride, testosterone were all Fluka compounds. *tert*-Butyldimethylsilylchloride and tetrabutylammoniumiodide were bought from Aldrich. Piperidine was purchased from Spectrochem. Pvt. Ltd, while ethylene glycol was from S.D. Fine Chem. Ltd. *p*-Methoxybenzyl chloride was obtained from Lancaster.

Preparation of (*R*)-(Benzyloxycarbonyl)phenylglycine **9:**⁴⁴ To an aqueous NaOH (30 mL, 1N) solution of (*R*)-phenylglycine (4.530 g, 30 mmol), carbobenzyloxy chloride (50% in toluene, 17 mL) and aq. solution of NaOH (1N, 50 mL) were added dropwise and alternately at 0 °C during 30 min. The reaction mixture was stirred for 1 h at 0 °C. The whole mixture was washed with cold ether (thrice) and the aq. layer was cooled again under icebath. It was acidified (pH~2) with 6N aq. HCl and was extracted with EtOAc (thrice). Combined organic layer was dried and condensed. The obtained mass was triturated with petroleum ether. Finally it was dried by azeotrope removal of water using dry benzene to get 8.1 g of the cbz-acid **9**: Yield 95%; mp 85 °C; [α]_D²⁵ -6.8° (*c* 5, CHCl₃); IR (KBr) 3350, 3060, 2980, 1710, 1460 cm⁻¹; ¹H NMR (CDCl₃, 60 MHz) δ 5.00 (s, 2H), 5.35 (bs, 1H), 6.80 - 7.50 (aromatics + NH, 11H), 8.80 (s, 1H, COOH).

General Procedure for the Preparation of the Amides 10: To a solution of (*R*)-cbz-phenylglycine **9** (3.0 g, 10.52 mmol), anhydrous CuCl₂ (1.70 g, 12.63 mmol) and 1-hydroxybenzotriazole (1.70 g, 12.63 mmol) in dry DMF (60 mL) at ice cold condition, was added dropwise a solution of DCC (2.6 g, 12.6 mmol) in DMF (10 mL) with vigorous stirring. After 20 min, the amine (21.65 mmol) was added and the reaction mixture was allowed to stir at 0 °C to rt during 20 h. Reaction mixture was diluted with EtOAc (100 mL) and washed with cold 0.1N HCl (100 mL), water, aq. NaHCO₃. The organic layer was dried and condensed. Column chromatography over silica gel afforded pure amide **10**.

(*R*)-1-[N-(Benzyloxycarbonyl)phenylglycyl]piperidine 10a: The **10a**⁴⁴ was prepared as a viscous liquid following the general procedure; Yield 90%; *R*_f 0.70 (2:5 EtOAc in petroleum ether); [α]_D²⁵ -100° (*c* 1.5, CHCl₃); IR (neat) 3410, 3300, 3040, 1715, 1635 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 0.8 - 1.8 (m, 6H), 3.06 - 3.9 (m, 4H), 5.03 (s, 2H), 5.50 (d, *J* = 9 Hz, 1H), 6.40 (d, *J* = 9 Hz, NH, 1H), 7.15 - 7.63 (aromatics, 10H).

(*R*)-1-[N-(Benzyloxycarbonyl)phenylglycyl]morpholine 10b: The N-cbz-amide **10b** was obtained as a viscous liquid following the general procedure; Yield 96%; *R*_f 0.53 (2:5 EtOAc in petroleum ether); [α]_D²⁵ -104.6° (*c* 1.5, CHCl₃); IR (neat) 3410, 3300, 1710, 1635 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 2.98 - 3.80 (m, 8H), 5.06 (s, 2H), 5.56 (d, *J* = 9 Hz, 1H), 6.46 (d, *J* = 9 Hz, NH, 1H), 7.16 - 7.50 (aromatics, 10H). Anal. calcd for C₂₀H₂₂N₂O₄: C, 67.79; H, 6.21; N, 7.90; Found: C, 66.90; H, 6.30; N, 8.01.

General Procedure for LAH reduction of N-cbz-Amides: The amide **10** (4 mmol) was dissolved in THF (30 mL), treated with LAH (8.0 mmol), and stirred under reflux for 6 h. Excess of LAH was destroyed by addition of 2-3 drops of EtOAc. Water (300 μ L) was added followed by the same amount of 4N NaOH. After 5 min, 900 μ L of water was again added and the mixture was stirred for 15 min. A white precipitate was filtered off, the filtrate was dried, and solvent was evaporated. The oily mass was taken in 15 mL diethyl ether. The whole was extracted with aq. HCl. The aq. layer was washed with ether, basified with 4N NaOH and was extracted with dichloromethane. The combined extracts were washed with brine, dried and then condensed to obtain the diamine **11** as colourless oil, which turns slowly yellowish on keeping for longer period in refrigerator.

(R)-N-Methyl-1-phenyl-2-piperidinoethanamine 11a: This was prepared as per the general procedure mentioned above; Yield 83%; $[\alpha]^{25}_{\text{D}} -91.6^{\circ}$ (*c* 1.8, CHCl_3) [lit.⁴⁵ $[\alpha]^{25}_{\text{D}} +109.1^{\circ}$ (*c* 1.88, CHCl_3) for *S*-isomer]; IR (neat) 3330, 3020 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.43 (m, 2H), 1.56 (m, 4H), 2.20 - 2.33 (m, 4H), 2.30 (s, 3H), 2.46 (t, *J* = 9 Hz, 2H), 2.56 (bs, NH , 1H), 3.63 (dd, *J* = 9 Hz, 3 Hz, 1H), 7.20 - 7.40 (aromatics, 5H); ^{13}C NMR (CDCl_3 , 75.469 MHz) δ 24.38, 26.06, 34.60, 54.69, 62.27, 66.61, 126.90, 127.32, 128.18, 142.63; MS (CI, *m/z*): 220 ($\text{M}^{++} 2$), 219 ($\text{M}^{++} 1$), 217, 188, 134, 120, 98 (base peak). Anal. calcd for $\text{C}_{14}\text{H}_{22}\text{N}_2$: C, 77.06; H, 10.0; N, 12.80; Found: C, 77.34; H, 10.40; N, 12.72.

(R)-N-Methyl-1-phenyl-2-morpholinoethanamine 11b: This was prepared as per the general procedure mentioned above; Yield 82%; $[\alpha]^{25}_{\text{D}} -92.0^{\circ}$ (*c* 1.2, CHCl_3); IR (neat) 3330, 3060, 3030 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 2.10 - 2.90 (m, 8H), 2.30 (s, 3H), 3.73 (m, 4H), 7.16 - 7.60 (aromatics, 5H); ^{13}C NMR (CDCl_3 , 75.469 MHz) δ 34.54, 53.71, 61.76, 66.18, 66.99, 127.14, 127.32, 128.31, 142.06; MS (CI, *m/z*): 222 ($\text{M}^{++} 2$), 221 ($\text{M}^{++} 1$), 219, 190, 134, 120, 100 (base peak). Anal. calcd for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}$: C, 70.90; H, 9.0; N, 12.70; Found: C, 71.32; H, 9.15; N, 12.9.

General procedure for the enantioselective deprotonation of cyclohexene oxide:

(i). *Titration of n-BuLi*⁴³: A very small amount of 1,10-phenanthroline (indicator) was taken in THF (1 mL). Then *n*-BuLi (500 μL) was added to it at 0 $^{\circ}\text{C}$. To this red coloured solution, 2-butanol was added dropwise till the colour changed to yellow at the neutralization point. The required amount of 2-butanol was found to be 80 μL , i.e, 0.872 mmol. So the calculated concentration of *n*-BuLi in hexane was 1.74 M.

(ii). *Deprotonation reaction*: *n*-BuLi (E-merck, 1.74 M in hexane, 2.2 mmol) was added to a solution of (*R*)-diamine **11** (2.45 mmol) in dry THF (10 mL) at 0 $^{\circ}\text{C}$. After 15 min of stirring, the cyclohexene oxide (200 μL , 2.0 mmol) was added and the mixture was stirred for 16 h (0 $^{\circ}\text{C}$ to rt). Most of the THF was removed in *vacuo* (40 mm Hg) at 0 $^{\circ}\text{C}$ and the reaction mixture was taken in ether (30 mL). It was washed with water, brine and dried. Solvent was removed in *vacuo* at 0 $^{\circ}\text{C}$ and the crude was chromatographed to provide pure (*S*)-2-cyclohexen-1-ol **16** as a colourless liquid. The spectral data for the (*S*)-**1** are given here for a typical experiment where (*R*)-**11a** was used as chiral amine; Yield 60%; $[\alpha]^{25}_{\text{D}} -121^{\circ}$ (*c* 1.5, CHCl_3) [lit.³ $[\alpha]^{25}_{\text{D}} +152.0^{\circ}$ (*c* 5, CHCl_3)

for *R*-isomer], [lit.⁴⁶ $[\alpha]^{25}_D +130.6^\circ$ (c 5, CHCl₃) for *R*-isomer]; ¹H NMR (CDCl₃, 400 MHz) δ 1.60 (m, 2H), 1.75 (m, 1H), 1.85 (s, 1H, -OH), 1.90 (m, 1H), 2.00 (m, 2H), 4.20 (s, 1H), 5.76 (m, 1H), 5.84 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 18.92, 25.01, 32.00, 65.44, 129.91, 130.40.

The above sample showed 80% ee. Similarly, when the diamine **11b** was used, (*S*)-**1** was obtained in 60% chemical yield and 77% ee.

Determination of enantiomeric purity of (*S*)-2-cyclohexen-1-ol.

(i). *Preparation of (R)-MTPA-Cl from the corresponding (S)-acid*¹⁶: The (*S*)-Mosher acid (872 mg, 3.72 mmol) was taken in petroleum ether (1 mL), and to that, oxalyl chloride (965 μ L, 11.17 mmol) followed by a catalytic amount of DMF were added under stirring condition. After 15 min, the reaction mixture was set for reflux for 1.5 h keeping the bath temperature at 80 °C. Excess of oxalyl chloride and petroleum ether were distilled under atm. pressure at 100 °C. Finally the (*R*)-MTPA-Cl was distilled (bp 120 °C at 2 mm Hg) and was kept under argon atmosphere.

(ii). *General procedure for making MTPA ester of (S)-1*: To a solution of (*S*)-**1** (5 mg), Et₃N (3 eq.) and a crystal of DMAP in dichloromethane (0.5 mL) was added (*R*)-MTPA-Cl (1.5 eq., 98% ee) at room temperature. Reaction mixture was allowed to stand until the starting material was fully consumed. If necessary, some more amount of MTPA-Cl and Et₃N were added to make sure that the reaction was complete. Reaction mixture was filtered through a short silica gel column to get the mixture of two diastereomeric MTPA esters **15**: ¹H NMR (CDCl₃, 400 MHz) δ 1.60 (m, 2H), 1.75-2.10 (bm, 4H), 3.50 (bs, 3H), 5.45 (m, 1H), 5.72 (m, *RS*-**15** from minor *R*-cyclohexenol), 5.81 (m, *SS*-**15** from major *S*-cyclohexenol), 5.85 - 6.00 (bm, 1H), 7.25 - 7.65 (bm, 5H, aromatics).

Based on above nmr data, the enantiomeric excess of (*S*)-cyclohexenol **1** is 78.5%. The optical purity of the (*S*)-Mosher acid is 98%. So corrected value of the optical purity of (*S*)-**1** is 80% using the CNLA base **13**. Similarly the CNLA base **14** gave (*S*)-**1** in 77% ee (Scheme IV).

Preparation of 3-cyclopenten-1-ol **16**¹⁷: To a THF (90 mL) solution of α -pinene (dried over CaH₂, 47 mL, 294.3 mmol), BH₃-DMS (13.2 mL, 133.8 mmol) was added at ice cold condition and was stirred at that temperature for 2 h. By this time, a white suspension was formed. Freshly distilled cyclopentadiene (18 mL, 267.2 mmol) was added at ice cold condition

and the reaction mixture was stirred for further 16 h (0 °C to rt). Reaction mixture was cooled again and the excess reagent was destroyed by adding few drops of water. Aq. NaOH solution (5.4 g in 45 mL H₂O) was added dropwise followed by 30% H₂O₂ (54 mL). It was stirred for 30 min. The aq. layer was salted out by adding NaCl (20 g). The THF layer was separated and condensed on rota evaporator. The resulting mass was diluted with ether (200 mL) and was stirred with 150 mL 1N AgNO₃ (26 g) for 30 min. Aqueous layer was separated and the organic layer was washed with aq. AgNO₃ solution. The combined aq. layer was washed again with ether. Then it was treated with excess NaCl at 0 °C with vigorous stirring for 15 min. It was extracted by diethyl ether (thrice) and the ether layer was dried and condensed (40 mm Hg). The crude material was distilled to get 3-cyclopenten-1-ol **16** as colourless liquid (3.38 g). Yield 30%; bp 65 °C at 35 mm Hg; *R*_f 0.3 (10% EtOAc in petroleum ether); IR (neat) 3350, 2920, 1420, 1315, 1280, 1190 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 2.40 (m, 4H), 3.16 (bs, 1H, -OH), 4.66 (heptate, *J* = 3 Hz, 1H), 5.80 (s, 2H).

Synthesis of *cis*- and *trans*-4-*tert*-butyldimethylsiloxy-1,2-epoxycyclopentane 19a and 20a: To a DMF (5 mL) solution of 3-cyclopenten-1-ol **16** (500 mg, 5.95 mmol) and imidazole (647 mg, 9.52 mmol), TBDMS-Cl (1.34 g, 8.92 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 12 h. It was diluted with EtOAc and was washed successively with water, brine and finally dried. Condensation of organic layer afforded the crude product **17** (1.4 g). This was dissolved in CH₂Cl₂ (35 mL) and *m*-CPBA (50%, 2.68 g, 7.77 mmol) was added in portions at 0 °C. After 4 h reaction was complete. The reaction mixture was washed with aq. Na₂SO₄, aq. NaHCO₃, water and brine. Finally the organic layer was dried and condensed. After column chromatography both the *cis*- and *trans*-epoxides, **19a** and **20a** were obtained in pure forms.

***cis*-4-*tert*-Butyldimethylsiloxy-1,2-epoxycyclopentane 19a:** Yield 48%; *R*_f 0.45 (5% EtOAc in petroleum ether); IR (neat) 3020, 2960, 1460, 1360, 1100 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 0.10(s, 6H), 0.90 (s, 9H), 2.00 (m, 4H), 3.36 (s, 2H), 4.40 (m, 4H).

***trans*-4-*tert*-Butyldimethylsiloxy-1,2-epoxycyclopentane 20a:** Yield 12%; *R*_f 0.60 (5% EtOAc in petroleum ether); IR (neat) 3050, 2980, 1460, 1280 cm⁻¹; ¹H NMR (CCl₄, 60 MHz)

80.10(s, 6H), 0.90 (s, 9H), 1.56 and 2.36 (ABX, $J = 14$ Hz, 7 Hz, 4H), 3.36 (s, 2H), 4.05 (qui, $J = 7$ Hz, 1H).

Synthesis of *cis*- and *trans*-4-tetrahydropyranyloxy-1,2-epoxycyclopentane 19b and 20b: To a dichloromethane solution (10 mL) of 3-cyclopenten-1-ol **16** (420 mg, 5 mmol) and pTsOH.H₂O (10 mg, cat.), DHP (900 μ L, 10 mmol) was added at 0 °C and the reaction mixture was stirred for 1 h. Tlc indicated the disappearance of the starting material. It was diluted with CH₂Cl₂, washed with aq. NaHCO₃, water, brine and finally dried. The crude product **18** (1.1 g) was dissolved in CH₂Cl₂ (30 mL) and was cooled at 0 °C. To that m-CPBA (50%, 2.485 g, 7.201 mmol) was added in portions with vigorous stirring. Reaction was complete after 5 h. Reaction mixture was worked up as mentioned earlier. Chromatography over silica gel led both *cis*- and *trans*- epoxides in pure form.

***cis*-4-Tetrahydropyranyloxy-1,2-epoxycyclopentane 19b^{11d}:** Yield 44%; R_f 0.30 (10% EtOAc in petroleum ether); IR (neat) 3040, 2940, 1440, 1200, 1140 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 1.60 (m, 6H), 1.95 (m, 4H), 3.30 (s, 2H), 3.20 - 4.00 (m, 2H), 4.23 (heptate, $J = 3$ Hz, 1H), 4.50 (m, 1H).

***trans*-4-Tetrahydropyranyloxy-1,2-epoxycyclopentane 20b^{11d}:** Yield 29%; R_f 0.55 (10% EtOAc in petroleum ether); IR (neat) 3030, 2950, 1450, 1390, 1080 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 1.80 (m, 6H), 2.38 (ABX, $J = 14$ Hz, 7 Hz, 2 Hz, 4H), 3.30 (s, 2H), 3.20 - 4.20 (m, 3H), 4.40 (m, 1H).

General procedure for enantioselective deprotonation of 3,4-epoxycyclopentanol derivatives 19 and 20: n-BuLi (E-Merck, 1.74 M in hexane, 2.0 mmol) was added to a solution of (*R*)-diamine (2.32 mmol) in the required solvent (10 mL) at 0 °C. After 15 min stirring, the epoxide **19** or **20** (2.0 mmol) was added and the mixture stirred (0 °C - rt) for the required period of time (see the schemes VII and VIII). Most of the solvent was removed in *vacuo* at 0 °C and the reaction mixture was taken up in ether (30 mL). The organic layer was washed with aq. tartaric acid, water, brine and dried. Solvent was removed in *vacuo* and the crude was chromatographed to provide pure allylic alcohol **8** or **22** as a colourless liquid.

***cis*-(1*S*, 4*R*)-4-*tert*-Butyldimethylsiloxy-2-cyclopenten-1-ol 8a^{8a}:** The **8a** was prepared as per the above general procedure. The spectral and physical data for the deprotonation

reaction in benzene, with the ligand **11a** is given as follows; Yield 66%; R_f 0.45 (10% EtOAc in petroleum ether) $[\alpha]^{25}_D +20.4^\circ$ (c 0.75, CHCl_3) [lit.^{11d} $[\alpha]_D +21.5^\circ$ (c 0.94, CHCl_3) for (1*S*, 4*R*)-**8a**]; IR (neat) 3350 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.50 (dt, $J = 10.2\text{ Hz, } 5.7\text{ Hz, } 1\text{H}$), 2.10 (s, 1H, -OH), 2.68 (dt, $J = 14.3\text{ Hz, } 5.7\text{ Hz, } 1\text{H}$), 4.58 (bs, 1H), 4.65 (m, 1H), 5.50 (dd, $J = 22.4\text{ Hz, } 5.6\text{ Hz, } 2\text{H}$).

The above sample showed 97% ee. Similarly when the diamine **11b** was used (1*S*, 4*R*)-**8a** was obtained in 60% chemical yield and 94% ee.

cis-(1*S*, 4*R*)-4-Tetrahydropyranyloxy-2-cyclopenten-1-ol **8b**^{8a}: The **8b** was prepared as per the above general procedure. The spectral and physical data for the deprotonation reaction in ether, with the ligand **11a** is given as follows: Yield 56%; R_f 0.30 (20% EtOAc in petroleum ether) $[\alpha]^{25}_D +29.7^\circ$ (c 1.0, CHCl_3) [lit.^{11d} $[\alpha]_D +27.3^\circ$ (c 0.77, CHCl_3) for (1*S*, 4*R*)-**8b**]; IR (neat) $3340, 2920, 1440, 1050\text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 400 MHz) δ 1.20 – 2.10 (m, 8H), 2.70 (ddt, $J = 37\text{ Hz, } 12\text{ Hz, } 6\text{ Hz, } 1\text{H}$), 3.53 (m, 1H), 3.90 (m, 1H), 4.63 (m, 2H), 4.75 (m, 1H), 6.03 (m, 2H).

The above sample had 56% ee.

trans-(1*S*, 4*S*)-4-*tert*-Butyldimethylsiloxy-2-cyclopenten-1-ol **22a**^{8a}: Deprotonation was done in ether using the ligand **11a** and the result is summarized here; Yield 35%; R_f 0.25 (40% EtOAc in petroleum ether) $[\alpha]^{25}_D -81.0^\circ$ (c 1.0, CHCl_3) [lit.^{11d} $[\alpha]_D -129^\circ$ (c 0.69, CHCl_3) for (1*S*, 4*S*)-**22a**]; IR (neat) $3350, 2930, 1440, 1050\text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 400 MHz) δ 0.1 (s, 6H), 0.9 (s, 9H), 1.4 - 1.7 (bs, 1H, -OH), 2.05 (m, 2H), 5.14 (bs, 1H), 5.10 (m, 1H), 5.95 (m, 2H).

The above sample showed 68% ee.

trans-(1*S*, 4*S*)-4-Tetrahydropyranyloxy-2-cyclopenten-1-ol **22b**: The **22b** was prepared as per the above general procedure. The spectral and physical data for the deprotonation reaction in ether, with the ligand **11a** is given as follows: Yield 52%; R_f 0.30 (20% EtOAc in petroleum ether) $[\alpha]^{25}_D -23.5^\circ$ (c 1.0, CHCl_3) [lit.^{11d} $[\alpha]_D -129^\circ$ (c 0.59, CHCl_3) for (1*S*, 4*S*)-**22b**]; IR (neat) $3340, 3040, 2920, 1440\text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 400 MHz) δ 1.40 – 1.90 (m, 6H + 1H for -OH), 1.97 - 2.30 (m, 2H), 3.52 (m, 1H), 3.90 (m, 1H), 4.68 (m, 1H), 5.02 (m, 2H), 6.07 (m, 2H).

Determination of Enantiomeric excess in the case of **8** and **22**.

Synthesis of (*S*)-MTPA ester: 5 mg of **8** or **22** was taken in 0.5 mL dry CH₂Cl₂ and to that a crystal of DMAP, triethylamine (2 eq. to alcohol) and 1.5 eq. of (*R*)-(+)- α -methoxy- α -trifluoromethylphenylacetyl chloride (MTPA-Cl) were added in an usual way to provide the mixture of two diastereomeric MTPA esters.

All the MTPA esters derived from (*1S*, *4R*)-**8a**, (*1S*, *4R*)-**8b**, (*1S*, *4S*)-**22a** and (*1S*, *4S*)-**22b** were analyzed on 400 MHz to determine the enantiomeric excess.

MTPA ester of (*1S*, *4R*)-8a**:** ¹H NMR (CDCl₃, 400 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.72 (dt, *J* = 14 Hz, 5 Hz, 1H), 2.87 (dt, *J* = 14 Hz, 8 Hz, 1H), 3.40 - 3.60 (m, 3H), 4.75 (m, 1H), 5.67 (m, 1H), 5.87 (d, *J* = 5.6 Hz, one diastereomer from (*1R*, *4S*)-**8a**), 5.96 (d, *J* = 5.6 Hz, other diastereomer from (*1S*, *4R*)-**8a**), 6.05 (d, *J* = 5.6 Hz, 1H), 7.35 - 7.65 (aromatics, 5H).

Considering the relative intensities of two diastereomeric protons at 5.87 ppm and 5.96 ppm (total integration is equal to one proton), the enantiomeric excess was found to be 95%. The optical purity of the (*S*)-Mosher acid is 98%. So corrected value of the optical purity of (*1S*, *4R*)-**8a** is 97% using the CNLA base **13** (Scheme VII).

Similarly the CNLA base **14** gave (*1S*, *4R*)-**8a** in 94% ee.

MTPA ester of (*1S*, *4R*)-8b**:** ¹H NMR (CDCl₃, 400 MHz) δ 1.40 - 2.00(m, 7H), 2.90 (m, 1H), 3.50 (m, 1H), 3.58 (s, 3H), 3.88 (m, 1H), 4.71 (m, 2H), 5.71 (bs, 1H), 5.97 (m, one diastereomer from (*1R*, *4S*)-**8b**), 6.05 (m, other diastereomer from (*1S*, *4R*)-**8b**), 6.20 (m, 1H), 7.30 - 7.60 (aromatics, 5H).

Considering the relative intensities of two diastereomeric protons at 5.97 ppm and 6.05 ppm (total integration is equal to one proton), the enantiomeric excess was found to be 55%. The optical purity of the (*S*)-Mosher acid is 98%. So corrected value of the optical purity of (*1S*, *4R*)-**8b** is 56% using the CNLA base **13** (Scheme VII).

MTPA ester of (*1S*, *4S*)-22a**:** ¹H NMR (CDCl₃, 400 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 2.05 - 2.16 (m, 1H), 2.18 (ddd, *J* = 14 Hz, 6.5 Hz, 2 Hz, one diastereomer from (*1S*, *4S*)-**22a**), 2.27 (ddd, *J* = 14 Hz, 6.5 Hz, 2 Hz, other diastereomer from (*1R*, *4R*)-**22a**), 3.50 (m, 3H), 5.03 (m, 1H), 6.00 (m, 2H), 6.10 (m, 1H), 7.30 - 7.60 (aromatics, 5H).

Considering the relative intensities of two diastereomeric protons at 2.18 ppm and 2.27 ppm (total integration is equal to one proton), the enantiomeric excess was found to be 67%. The optical purity of the (*S*)-Mosher acid is 98%. So corrected value of the optical purity of (1*S*, 4*S*)-**22a** is 68% using the CNLA base **13** (Scheme VIII).

MTPA ester of (1*S*, 4*S*)-22b****: ¹H NMR (CDCl₃, 400 MHz) δ 1.50 - 1.85 (m, 6H), 2.15 - 2.26 (m, 1H), 2.29 (t, *J* = 4 Hz, one diastereomer from (1*S*, 4*S*)-**22b**), 2.33 (m, other diastereomer from (1*R*, 4*R*)-**22b**), 3.40 - 3.60 (m, 3H), 3.88 (m, 1H), 4.68 (m, 1H), 4.97 (s, 1H), 6.00 - 6.15 (m, 2H), 6.25 (m, 1H), 7.35 - 7.65 (aromatics, 5H).

Considering the relative intensities of two diastereomeric protons at 2.29 ppm and 2.33 ppm (total integration is equal to one proton), the enantiomeric excess of (1*S*, 4*S*)-**22b** was found to be 21% (Scheme VIII).

General Procedure for the Preparation of TBDMS Ethers:¹⁸ A solution of alcohol (2.0 mmol), imidazole (3.0 mmol), and TBDMS-Cl (3.0 mmol) in anhydrous DMF (2 mL) was stirred at r.t. for 12 h. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried and concentrated in *vacuo*. The crude was purified over silica gel.

Menthol TBDMS ether **26** (Table 2; entry 1): Yield 95% as a colourless liquid⁴⁷; *R*_f 0.9 (Petroleum ether); IR (film) 1070 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 0.6 - 2.5 (bm, 18H), 3.4 (m, 1H).

Geraniol TBDMS ether **27** (Table 2; entry 2): Yield 95% as a colourless liquid⁴⁸; *R*_f 0.9 (1:9 EtOAc in petroleum ether); IR (film) 1070 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.6 (m, 9H), 2.03 (s, 4H), 4.16 (d, *J* = 6.0 Hz, 2H), 5.16 (m, 2H).

Methyl Ricinoleate TBDMS ether **28** (Table 2; entry 3): Yield 96% as a colourless liquid⁴⁹; *R*_f 0.7 (5% EtOAc in petroleum ether); IR (film) 1735, 1075 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 0.10 (s, 6H), 0.86 (bs, 12H), 1.36 (bs, 18H), 2.1 (m, 8H), 3.56 (s, 4H), 5.4 (m, 2H).

Decanol TBDMS ether **29** (Table 2; entry 4): Yield 96% as a colourless liquid^{21c}; *R*_f 0.9 (1:9 EtOAc in petroleum ether); IR (film) 1060 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 12H), 1.33 (s, 16H), 3.6 (t, *J* = 6.0 Hz, 2H).

TBDMS ether of Cyclopent-3-en-1-ol 30 (Table 2; entry 5): Yield 96% as a colourless liquid⁵⁰; R_f 0.9 (1:9 EtOAc in petroleum ether); IR (film) 1070 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 2.33 (m, 4H), 4.5 (m, 1H), 5.63 (s, 2H).

Phenylethanol TBDMS Ether 31 (Table 2; entry 6): Yield 94% as a colourless liquid⁵¹; R_f 0.9 (1:9 EtOAc in petroleum ether); IR (film) 1090 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.46 (d, $J = 7.0$ Hz, 3H), 4.93 (q, $J = 7.0$ Hz, 1H), 7.26 (aromatics, 5H).

TBDMS Ether of Benzyl Alcohol 32 (Table 2; entry 7): Yield 95% as a colourless liquid⁵²; R_f 0.9 (1:9 EtOAc in petroleum ether); IR (film) 1095 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 4.7 (s, 2H), 7.26 (aromatics, 5H).

General Procedure for the Preparation of Tetrahydropyranyl Ethers: A solution of alcohol (2.0 mmol), 3,4-dihydro-2H-pyran (3.0 mmol), and a catalytic amount of $p\text{-TsOH}\cdot\text{H}_2\text{O}$ in anhydrous CH_2Cl_2 (5.0 mL) was kept at r.t. for 12 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried and concentrated in *vacuo*. The crude was purified over silica gel column chromatography.

Menthol THP Ether 33 (Table 3; entry 1): Yield 75% as a colourless liquid⁵³; R_f 0.65 (5% EtOAc in petroleum ether); IR (film) 1030, 1180 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.70 (s, 3H), 0.90 (d, $J = 7$ Hz, 6H), 1.1 - 2.5 (bm, 15H), 3.50 (m, 3H), 4.63 (m, 1H).

Geraniol THP Ether 34 (Table 3; entry 2): Yield 80% as a colourless liquid⁵⁴; R_f 0.77 (1:9 EtOAc in petroleum ether); IR (film) 1025, 1120 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.60 (bs, 15H), 2.10 (s, 4H), 3.80 (m, 4H), 4.63 (m, 1H), 5.23 (m, 2H).

Methyl Ricinoleate THP Ether 35 (Table 3; entry 3): Yield 60% as a liquid⁵⁴; R_f 0.52 (5% EtOAc in petroleum ether); IR (film) 1130, 1735 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.88 (m, 3H), 1.45 (m, 24H), 2.15 (m, 8H), 3.50 (m, 3H), 3.60 (s, 3H), 4.60 (bs, 1H), 5.40 (m, 2H).

Decanol THP Ether 36 (Table 3; entry 4): Yield 80% as a colourless liquid⁵⁵; R_f 0.74 (1:9 EtOAc in petroleum ether); IR (film) 1040, 1130 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.86 (m, 4H), 1.50 (m, 22H), 3.50 (m, 3H), 4.60 (s, 1H).

Testosterone THP Ether 37⁵⁶ (Table 3; entry 5): Yield 80%; R_f 0.50 (1:4 EtOAc in petroleum ether); IR (KBr) 1130, 1660 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.55 (m, 31H), 3.60 (m, 3H), 4.63 (s, 1H), 5.30 (s, 1H).

Phenylethanol THP ether 38 (Table 3; entry 6): Yield 75 % as a colourless liquid⁵³; R_f 0.82 (1:9 EtOAc in petroleum ether); IR (film) 1120 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.50 (m, 9H), 3.50 (m, 2H), 4.20 (bs, 1H), 4.60 (m, 1H), 7.10 (aromatics, 5H).

THP Ether of Benzyl Alcohol 39 (Table 3; entry 7): Yield 88 % as a colourless liquid⁵³; R_f 0.58 (1:9 EtOAc in petroleum ether); IR (film) 1120 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.70 (m, 6H), 3.65 (m, 2H), 4.56 (m, 3H), 7.30 (aromatics, 5H).

TBDMS Ether 42 (Scheme IX): Methyl ricinoleate THP ether **35** (*vide infra*) was treated with LAH (2 equivalent) in THF at 0 °C for 5 h. Excess LAH was destroyed with EtOAc. 2-3 Drops of water was added, followed by 7-8 drops of 4N NaOH and then 3-4 drops of water. It was stirred at rt for 20 min. and filtered. Solvent removal and purification over silica gel provided pure alcohol **41** which was converted into TBDMS ether **42** using the above mentioned general procedure.

Alcohol 41: Yield >98%; R_f 0.33 (1:9 EtOAc in petroleum ether); IR (film) 3380, 2930, 2860, 1020 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.88 (m, 3H), 1.45 (m, 24H), 2.15 (m, 8H), 3.65 (m, 5H), 4.63 (bs, 1H), 5.4 (m, 2H).

TBDMS Ether 42: Yield 92% as a colourless liquid; R_f 0.78 (1:9 EtOAc in petroleum ether); IR (film) 1100, 1020 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 12H), 1.45 (m, 24H), 2.15 (m, 8H), 3.65 (m, 5H), 4.63 (bs, 1H), 5.40 (m, 2H).

Ketal TBDMS ether 46 (Scheme X): Methyl ricinoleate **40** (1.60 mmol) was added at one shot to a stirring mixture of pyridiniumchlorochromate (6.40 mmol), NaOAc (6.40 mmol) and 4Å molecular sieves in CH_2Cl_2 (5 mL). The reaction mixture was further stirred for 3 h. The organic layer was washed with NaHCO_3 and water. It was dried and condensed. The precipitate obtained was washed with petroleum ether several times. The combined petroleum ether layer was condensed to get pure ketone **43**. The ketone **43**⁵⁷ (1.36 mmol), ethylene glycol (6.78 mmol), and catalytic amount of p-TsOH.H₂O were taken in benzene (10 mL) and refluxed for 12 h using Dean-Stark trap for removal of water. The flask was cooled, the benzene solution was diluted with EtOAc, washed with aq. NaHCO_3 solution, water, and dried. Solvent removal gave ketal ester **44** which was treated with LAH in ether for 3 h at 0 °C in the usual way. It was worked-up as above. Solvent removal and purification over silica gel provided pure ketal alcohol **45** which was converted into TBDMS ether **46** using the above mentioned general procedure method.

Ketone 43: Yield 84%; R_f 0.55 (5% EtOAc in petroleum ether); IR (neat) 2940, 1735, 1710 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.88 (m, 3H), 1.40 (bs, 18H), 2.10 (m, 8H), 3.06 (d, $J = 5$ Hz, 2H), 3.60 (s, 3H), 5.56 (t, $J = 5$ Hz, 2H).

Ketal Ester 44: Yield 65%; R_f 0.56 (5% EtOAc in petroleum ether); IR (neat) 1735 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.86 (m, 3H), 1.45 (bs, 18H), 2.15 (m, 8H), 3.60 (s, 3H), 3.83 (s, 4H), 5.40 (m, 2H).

Ketal Alcohol 45: Yield 94%; R_f 0.10 (5% EtOAc in petroleum ether); IR (film) 3380 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.88 (m, 3H), 1.40 (bs, 18H), 2.10 (m, 8H), 3.56 (t, $J = 5$ Hz, 2H), 3.83 (s, 4H), 5.40 (m, 2H).

Ketal TBDMS Ether 46: Yield 97% as a colourless liquid; R_f 0.9 (1:9 EtOAc in petroleum ether); IR (film) 1100 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 12H), 1.45 (bs, 18H), 2.15 (m, 8H), 3.66 (t, $J = 5$ Hz, 2H), 3.9 (s, 4H), 5.46 (m, 2H).

3-*t*-Butyldimethylsiloxy-5-tetrahydropyranyloxy-1-cyclopentene 25 (Scheme XI): To a LDA solution in THF (5 mL), prepared from diisopropylamine (1.03 mmol) and *n*-BuLi (1.74 M, 0.934 mmol), the epoxide **19a** (0.467 mmol) was added at 0 °C. THF was removed and diluted with ether. Organic layer was washed with water and dried. Column chromatography of the condensed material gave pure allylic alcohol **8** which was converted into THP ether **25** using the general procedure method.

4-*tert*-Butyldimethylsiloxy-2-cyclopenten-1-ol 8: Yield 79%; R_f 0.38 (1:9 EtOAc in petroleum ether); IR (neat) 3400, 1020 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.16 - 1.63 (m, 1H), 2.30 - 2.83 (m, 1H), 2.90 (s, 1H, OH), 4.30 - 4.73 (m, 2H), 5.60 - 6.00 (m, 2H).

3-*t*-Butyldimethylsiloxy-5-tetrahydropyranyloxy-1-cyclopentene 25: Yield 60%; R_f 0.76 (1:9 EtOAc in petroleum ether); IR (neat) 1020 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.20 - 1.90 (m, 7H), 2.30 - 2.83 (m, 1H), 3.20 - 4.00 (m, 2H), 4.26 - 4.93 (m, 3H), 5.60 - 6.00 (m, 2H).

1-*tert*-Butyldimethylsiloxy-3-tetrahydropyranyloxypropane 48 (Scheme XII): To a DMF (10 mL) solution of propane-di-ol (1 g, 13.14 mmol) and imidazole (983 mg, 14.45 mmol), TBDMS-Cl (2 g, 13.14 mmol) was added at ice cold condition. The whole reaction mixture was

stirred at room temperature for 12 h and worked up according to the general procedure to get the TBDMS ether **47**. This was converted to **48** using the general procedure method.

3-tert-Butyldimethylsiloxy-1-propanol 47: Yield 32%; R_f 0.47 (5% EtOAc in petroleum ether); IR (neat) 3380, 1460, 1250, 1110, 1045 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 3.70 (s, 6H).

1-tert-Butyldimethylsiloxy-3-tetrahydropyranyloxypropane 48: Yield 70%; R_f 0.55 (5% EtOAc in petroleum ether); IR (neat) 1125 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.50 (m, 6H), 3.20 - 3.96 (m, 8H), 4.60 (s, 1H).

Ketal THP Ether 51 (Scheme XIII): Mono ethylene ketal of 1,4-cyclohexanedione **49** (3.2 mmol) was taken in methanol (2 mL) and treated with NaBH_4 (4.8 mmol) at 0 °C for 1 h. Most of the methanol was removed in *vacuo* and the crude was taken in EtOAc. It was washed with water and dried. Solvent removal gave alcohol **50** which was converted into THP ether **51** using the general procedure method.

Ketal Alcohol 50: Yield 60%; R_f 0.25 (40% EtOAc in petroleum ether); IR (film) 3430 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.55 (m, 8H), 2.0 (s, 1H), 3.60 (m, 1H), 3.83 (s, 4H).

Ketal THP Ether 51: Yield 70 %; R_f 0.60 (80:20 Pet.-ether : EtOAc); IR (film) 1110 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.6 (m, 14H), 3.6 (m, 3H), 3.83 (s, 4H), 4.66 (bs, 1H).

p-Methoxybenzyl ether 53 (Scheme XIV): Methyl ricinoleate TBDMS ether **28** (*vide infra*) was treated with LAH (2 equivalent) in THF at 0 °C for 5 h. Excess LAH was destroyed with EtOAc. 2-3 Drops of water was added, followed by 7-8 drops of 4N NaOH and then 3-4 drops of water. It was stirred at rt for 20 min. and filtered. Solvent removal and purification over silica gel provided pure alcohol **52**. The alcohol (0.251 mmol) was taken with NaH (0.376 mmol) in THF (1 mL) and stirred for 1h. Then Bu_4NI (cat.) and p-methoxybenzyl chloride (0.376 mmol) were added. The reaction mixture was refluxed for 20 h under N_2 . It was filtered through cotton, condensed and then column chromatographed to get the p-methoxybenzyl ether **53**.

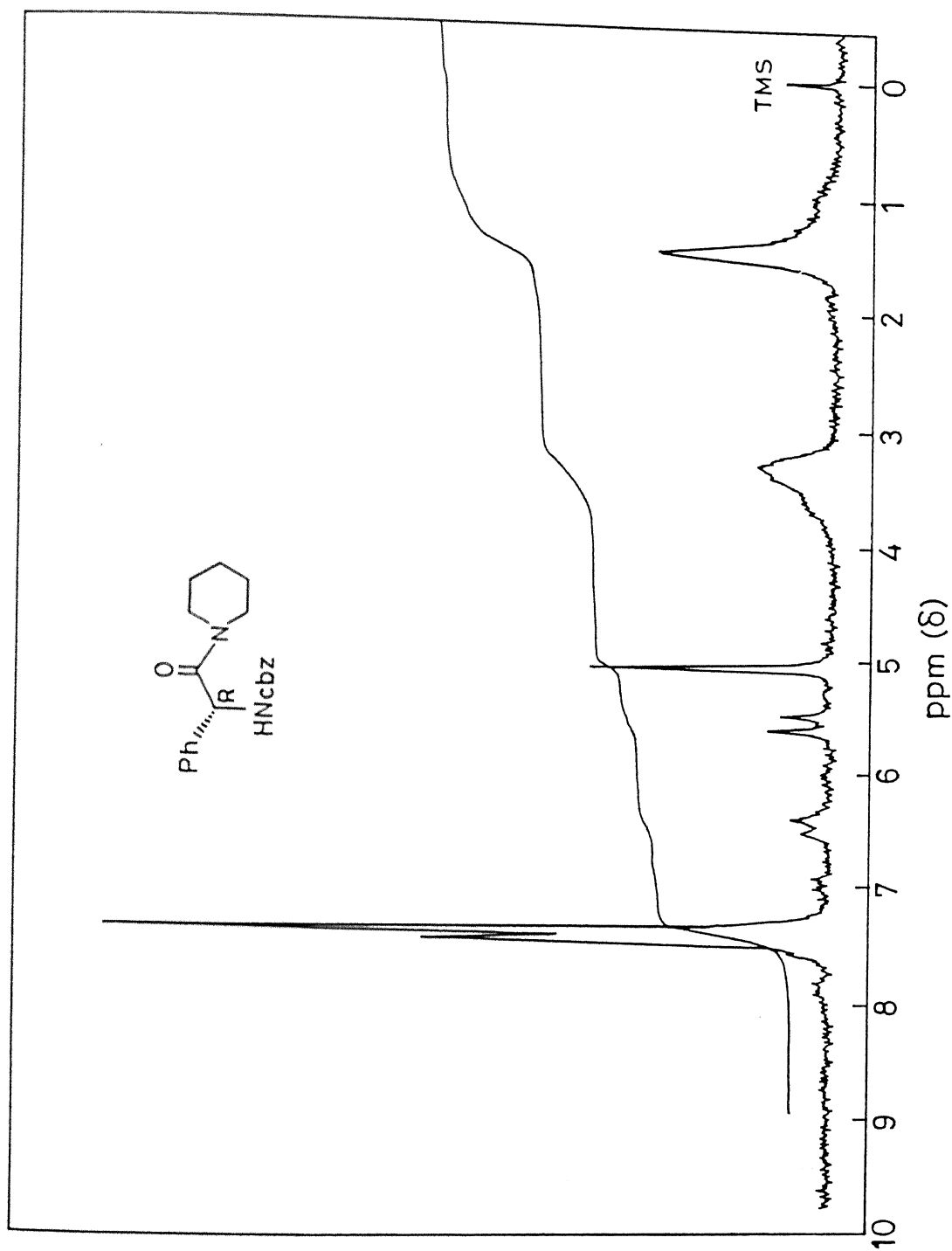
Alcohol 52: Yield 97%; R_f 0.43 (1:9 EtOAc in petroleum ether); IR (neat) 3400, 1070 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 15H), 1.40 (bs, 18H), 1.80 - 2.40 (m, 8H), 3.60 (t, $J = 5$ Hz, 3H), 5.20 - 5.60 (m, 2H).

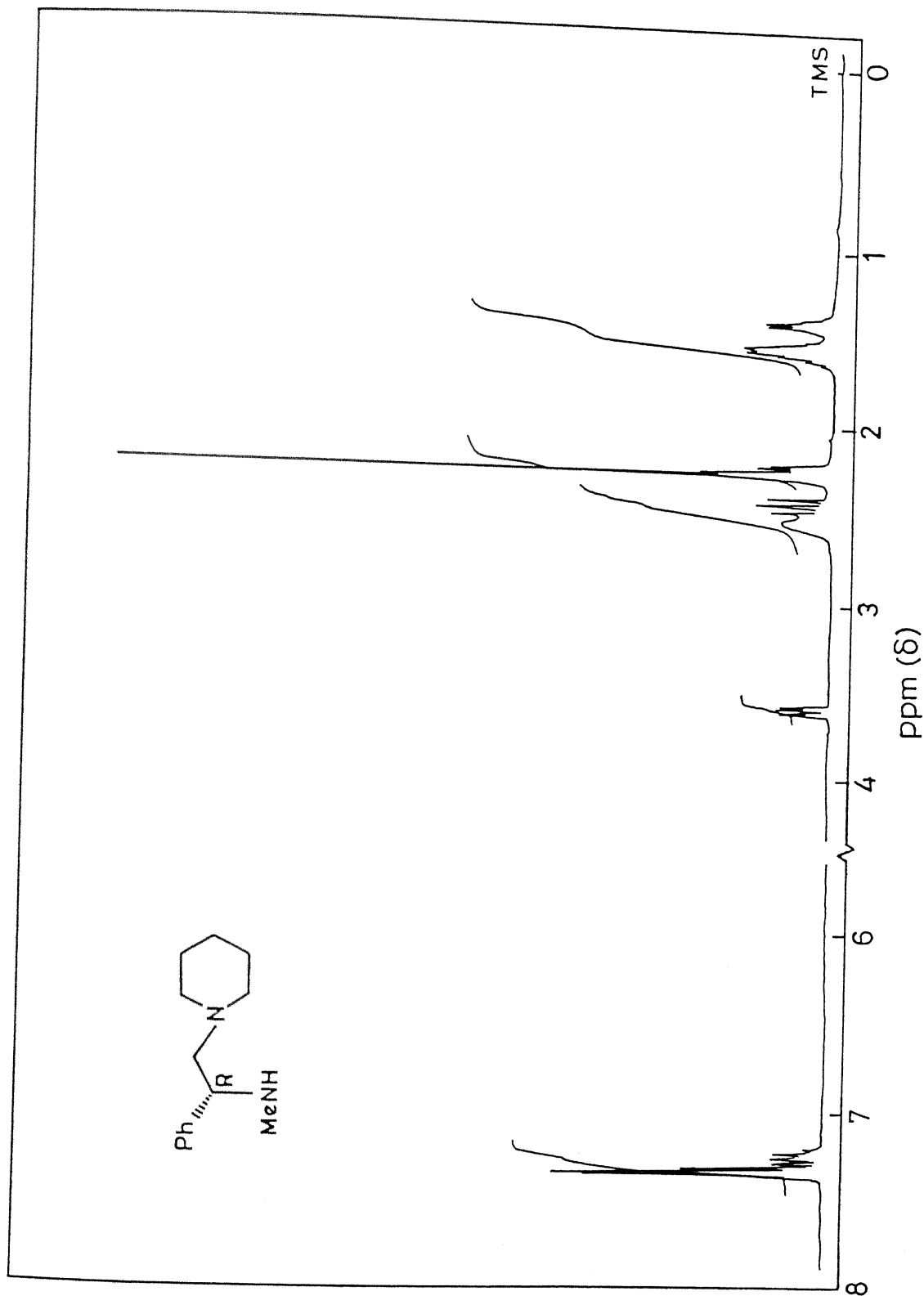
p-Methoxybenzyl ether **53**: Yield 46%; R_f 0.68 (5% EtOAc in petroleum ether); IR (neat) 3000, 1240, 1070 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.10 (s, 6H), 0.90 (s, 15H), 1.33 (bs, 18H), 1.70 - 2.36 (m, 8H), 3.33 (t, $J = 5$ Hz, 3H), 3.50 (m, 1H), 3.76 (s, 3H), 4.36 (s, 2H), 5.36 (t, $J = 4$ Hz, 2H), 6.96 (dd, $J = 12$ Hz, 9 Hz, 4H).

General procedure for Deprotection Reaction of TBDMS and THP ethers: A solution of TBDMS or THP ether (1 mmol) in methanol (4 - 5 ml) was treated with CAN (1.2 mmol, unless otherwise mentioned) at 0 °C and the red-coloured complex solution was stirred. The reaction was monitored by tlc. After the reaction was complete, the solvent was removed in vacuo at rt. The crude material was taken in ether, washed with aq. NaHCO_3 , water, and brine. After drying and solvent removal, the crude product was chromatographed over silica gel. The alcohol obtained was identical with the authentic sample by tlc, ^1H NMR, and IR. The results are summarized in the tables 2, 3, and 4.

9-Octadecen-1,12-diol **54**: Yield 96%; R_f 0.26 (20% EtOAc in petroleum ether); IR (neat) 3360, 1700 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 0.88 (m, 3H), 1.30 (bs, 18H), 1.70 - 2.36 (m, 8H), 3.56 (m, 5H), 5.43 (m, 2H).

1-Cyclopenten-3,5-diol **55**: Yield 90%; IR (neat) 3400 cm^{-1} ; ^1H NMR (CCl_4 , 60 MHz) δ 1.16 - 1.63 (m, 1H), 2.30 - 2.83 (m, 1H), 2.60 (s, 2H, OH), 4.33 - 4.76 (m, 2H), 5.60 - 6.00 (m, 2H).

60 MHz ¹H NMR spectrum of *(R)*-10a in CCl₄.

300 MHz ^1H NMR spectrum of (R)-11a in CDCl_3 .

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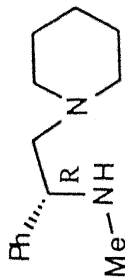
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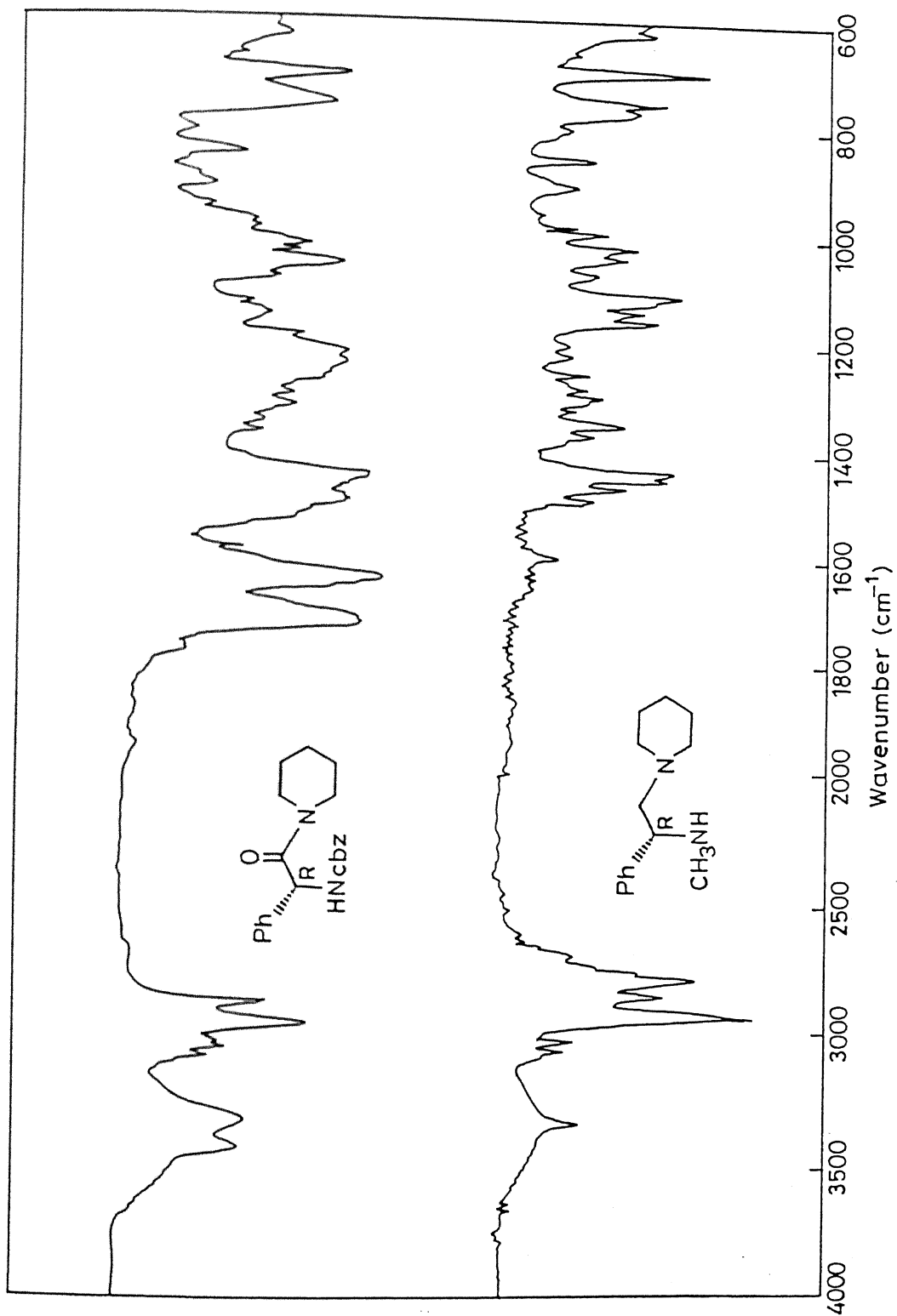
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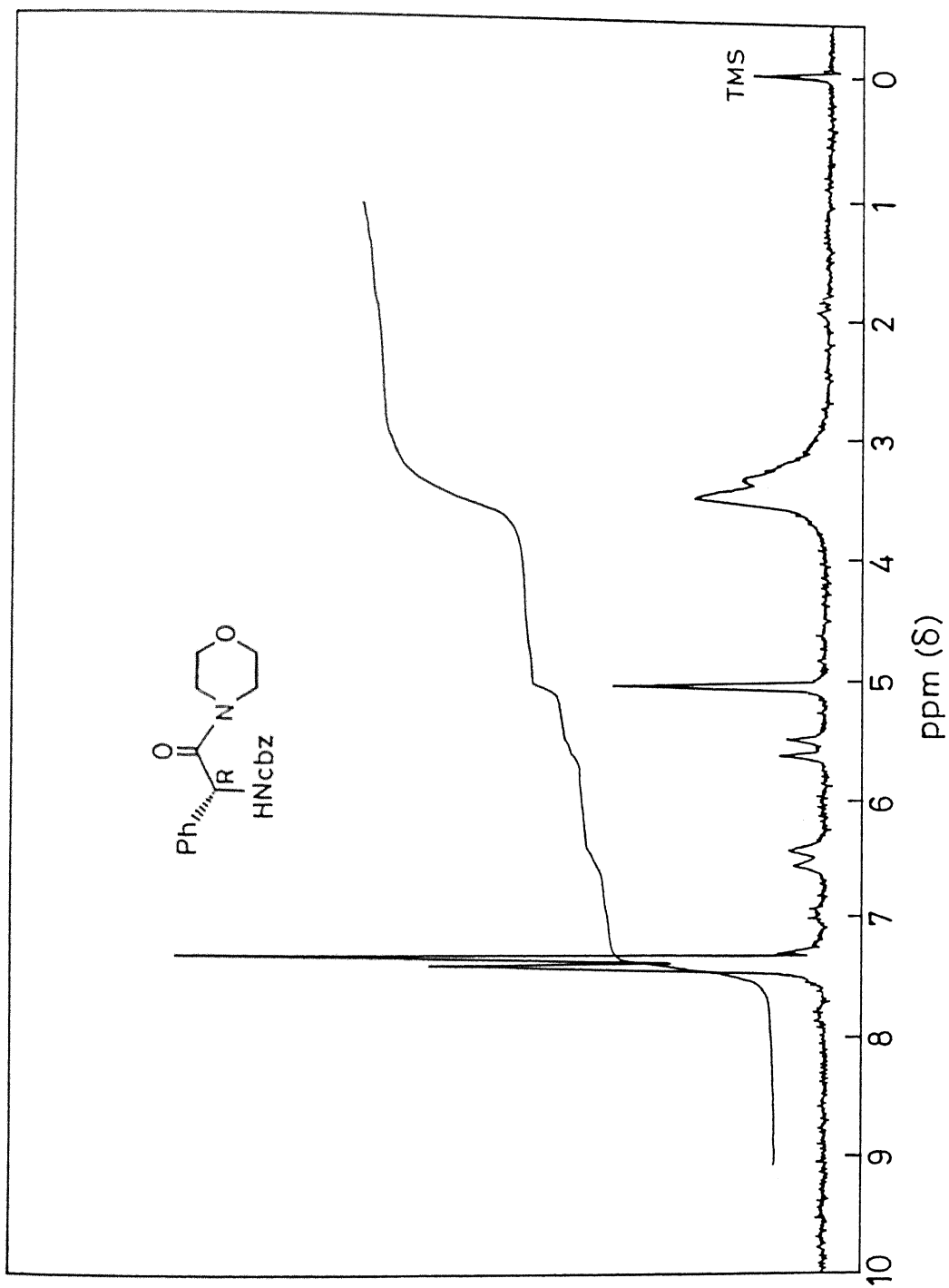
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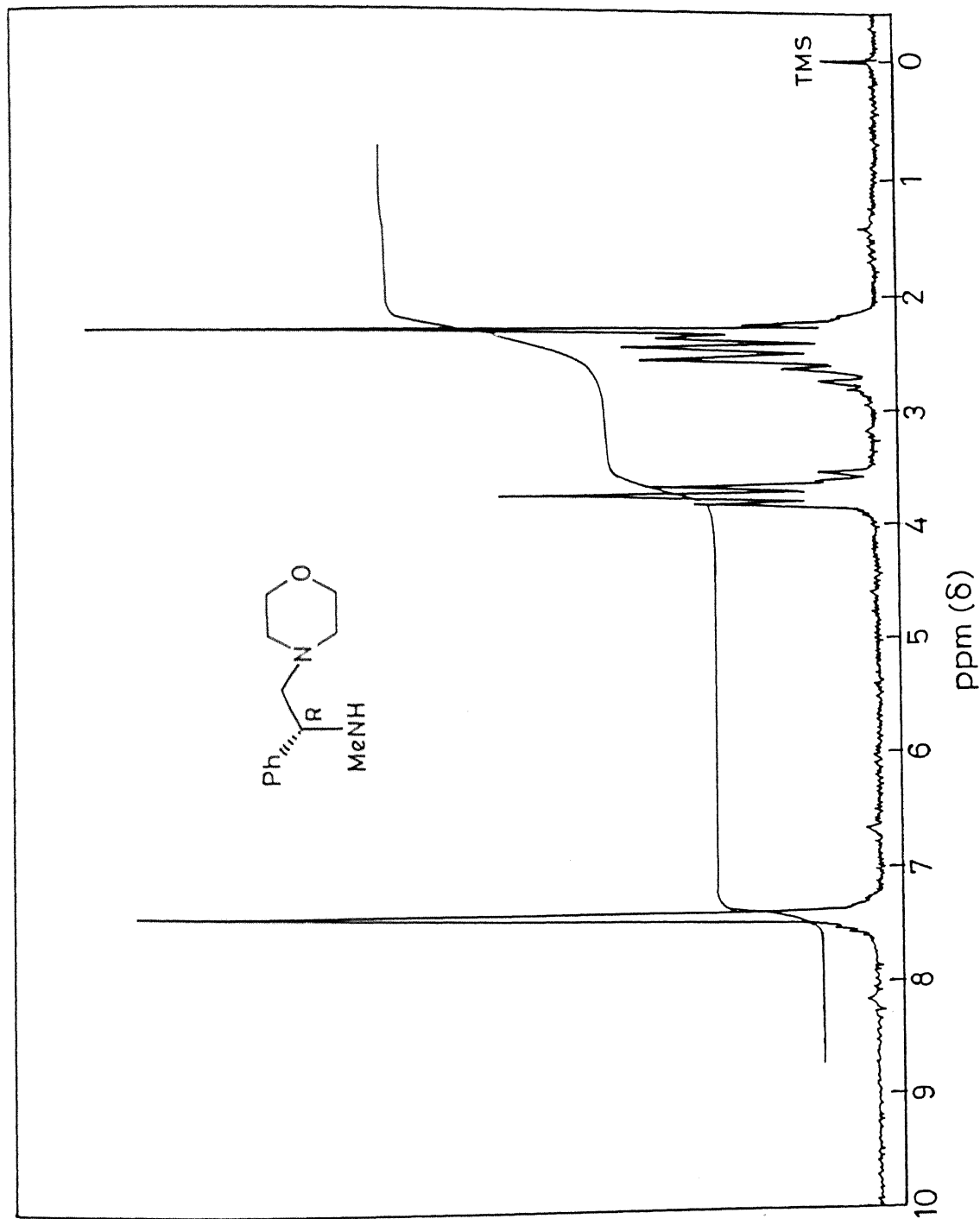
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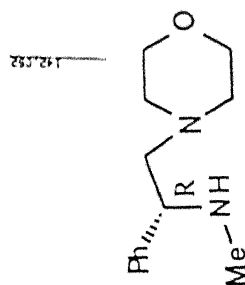




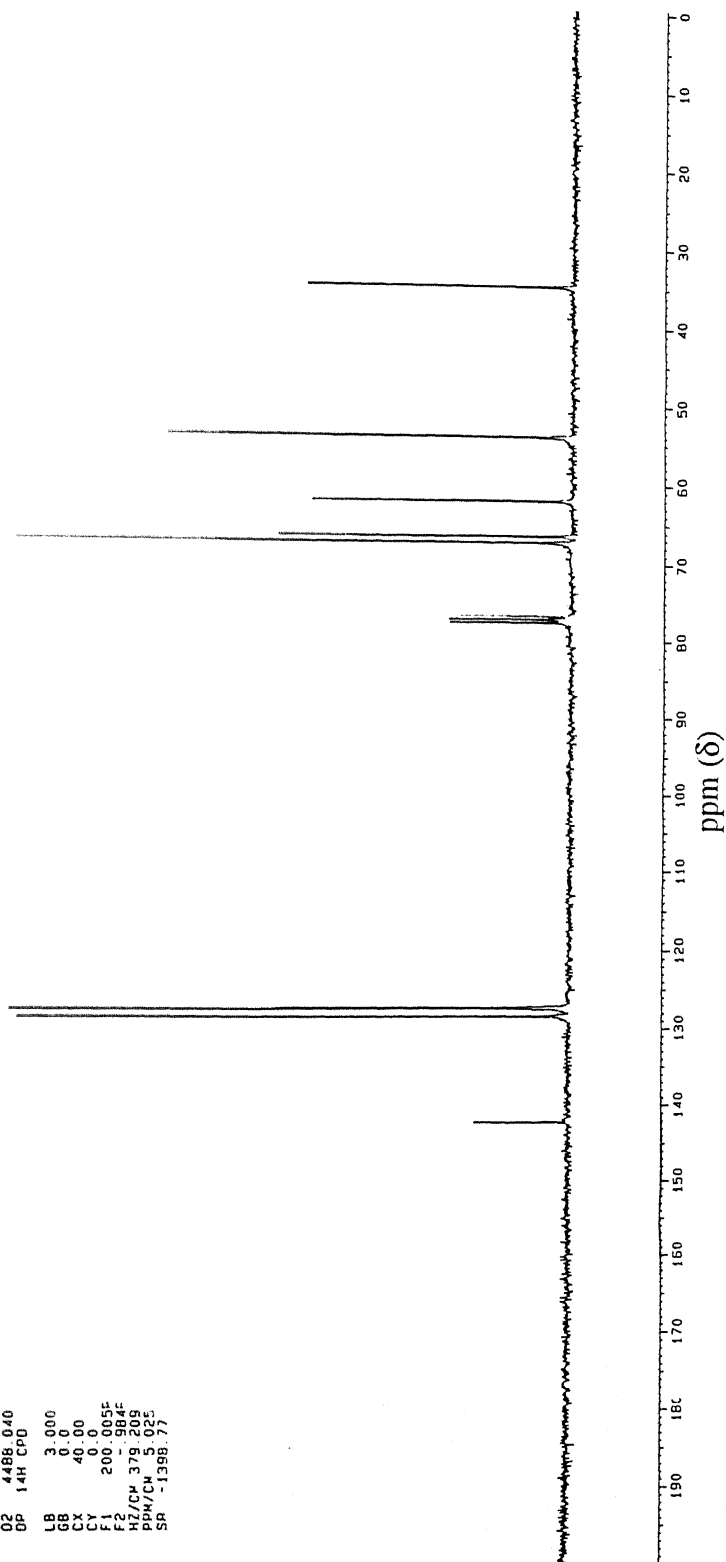
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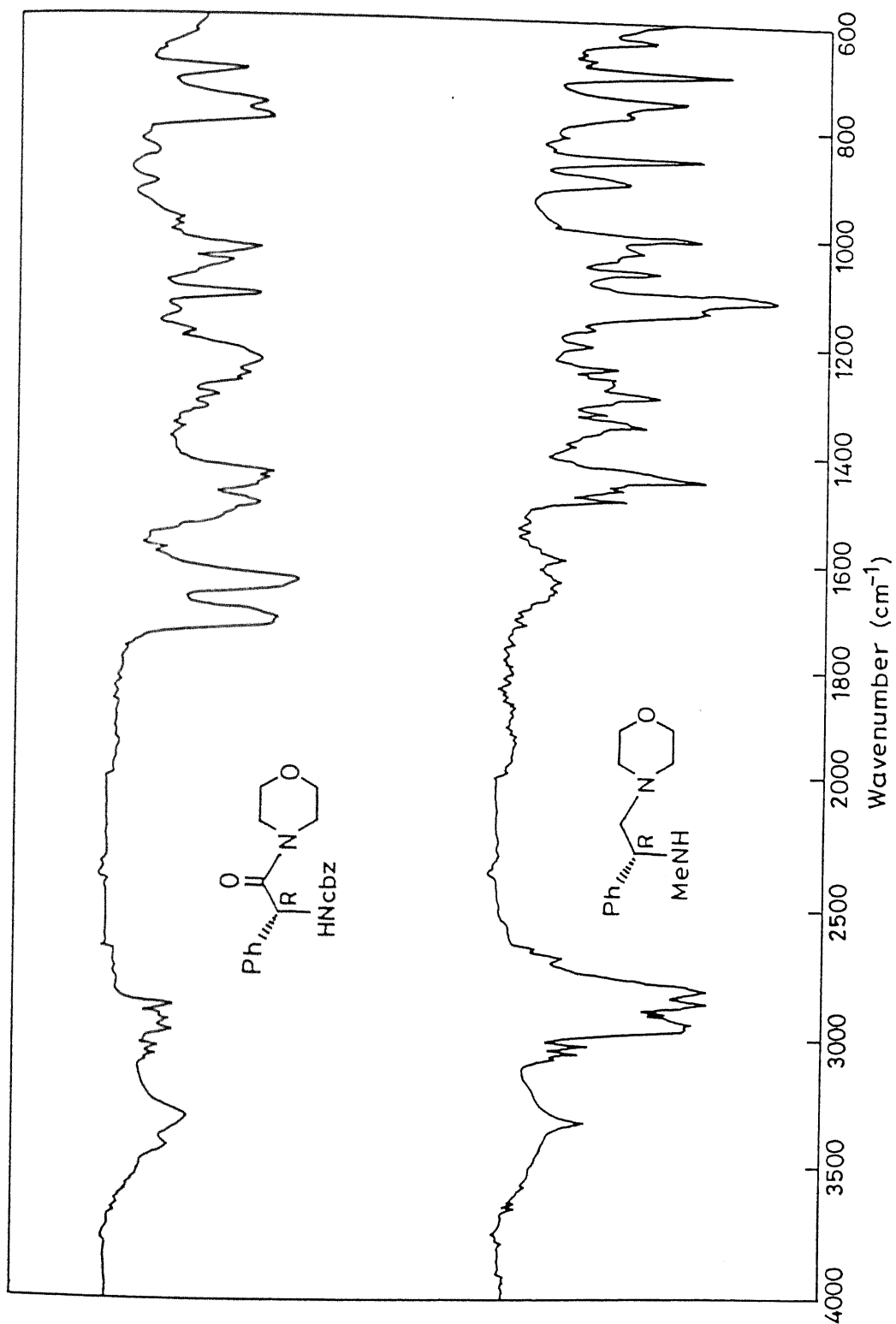
60 MHz ^1H NMR spectrum of (R)-11b in CCl_4 .

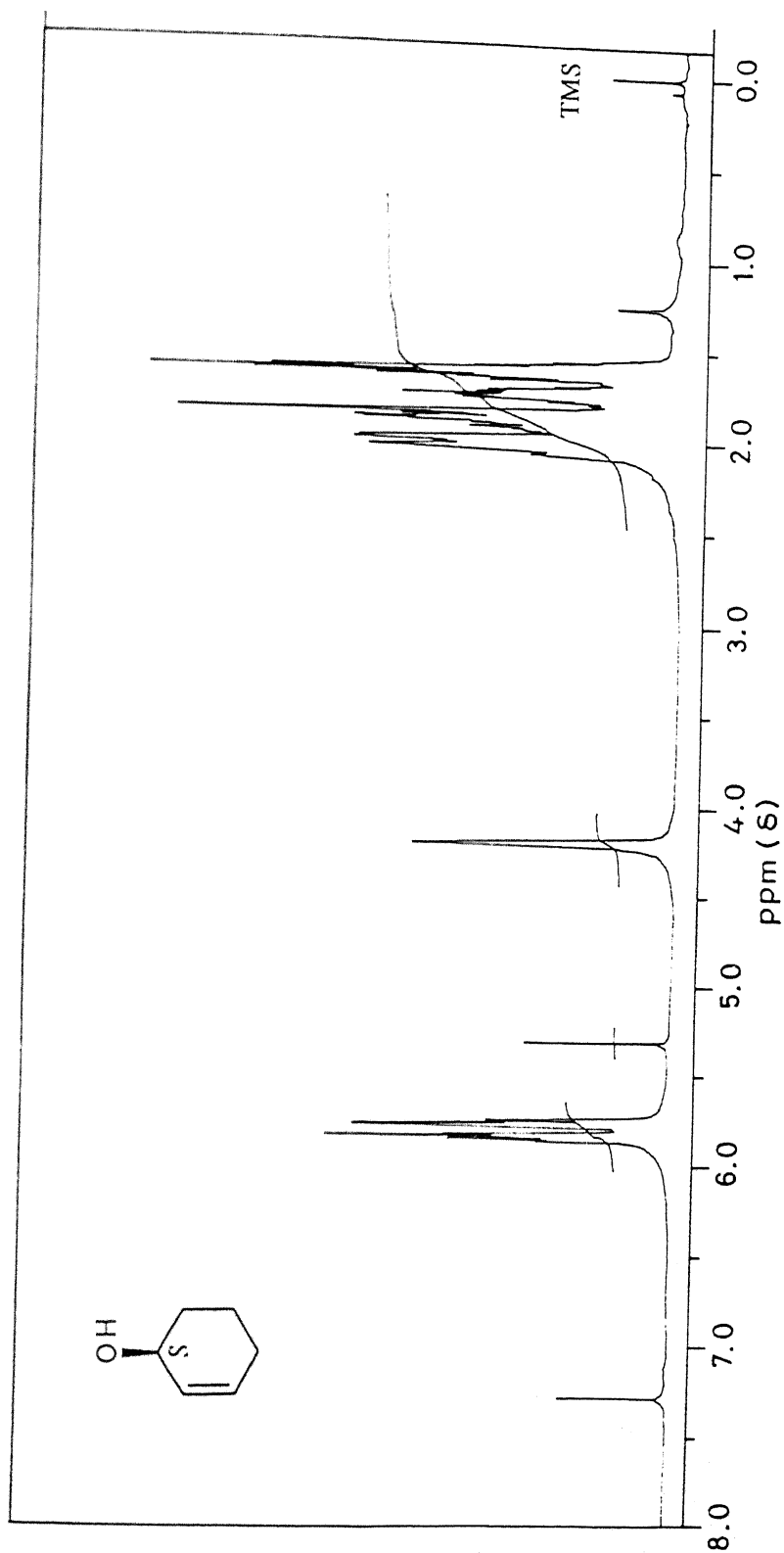


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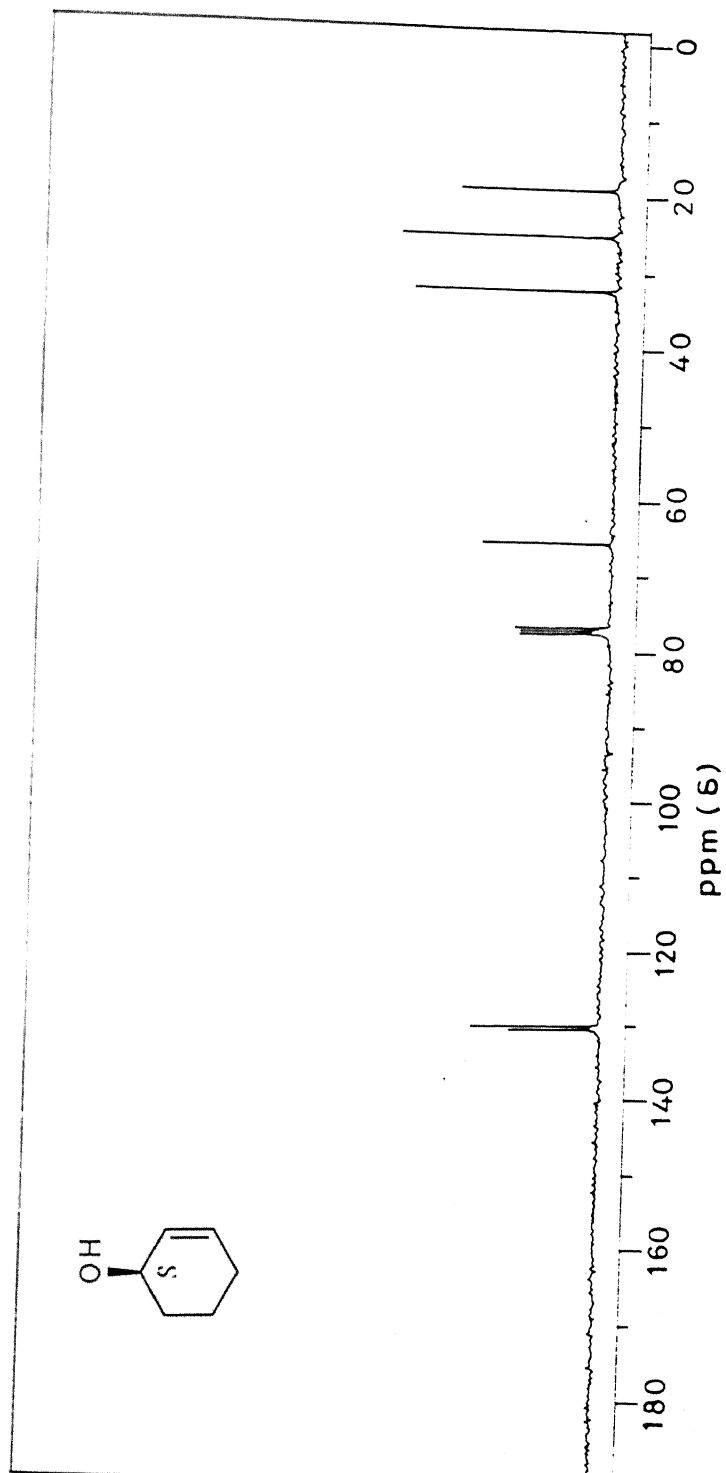


75.469 MHz ¹³C NMR spectrum of (R)-11b in CDCl₃.

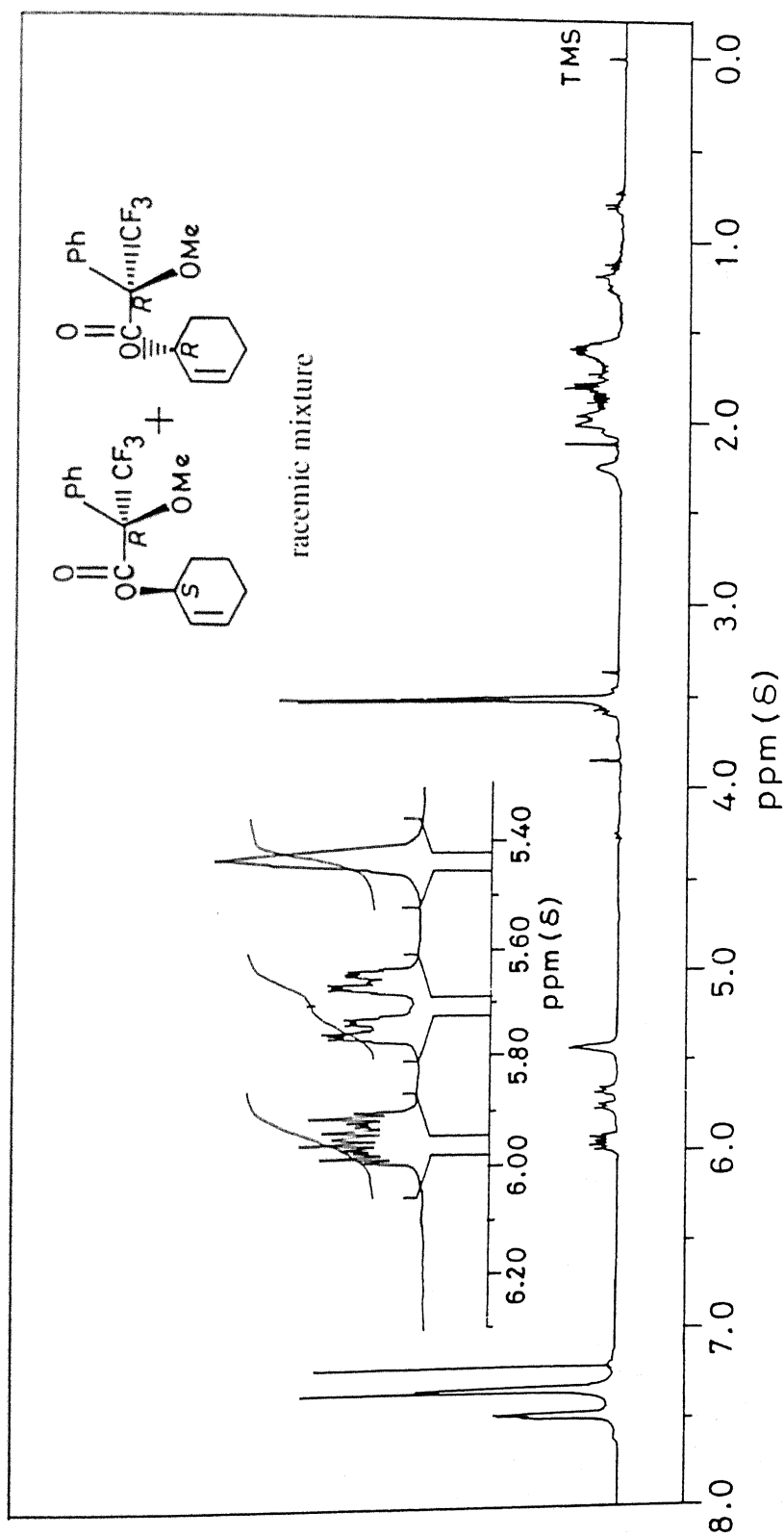


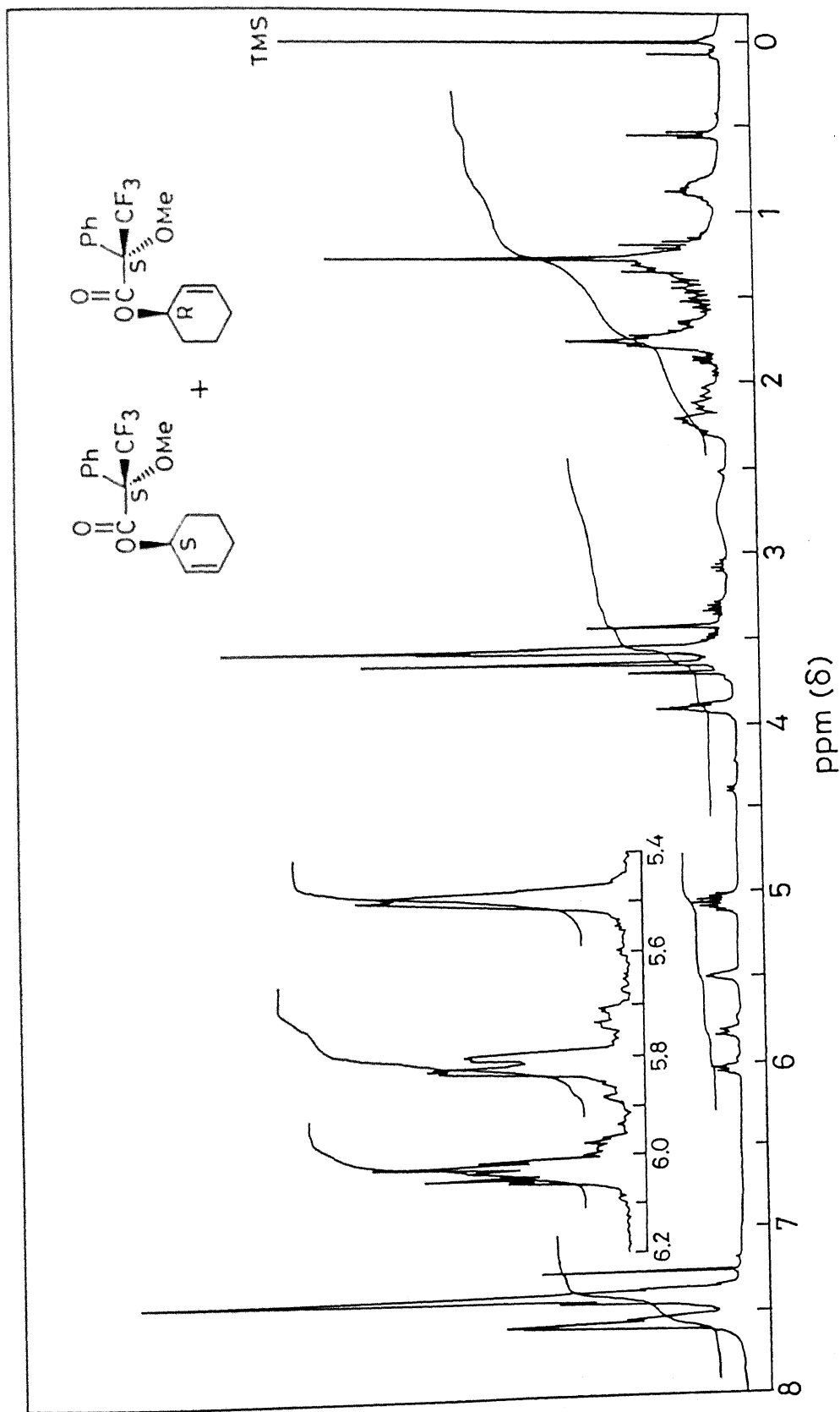


400 MHz ^1H NMR spectrum of (*S*)-**1** in CDCl_3 .

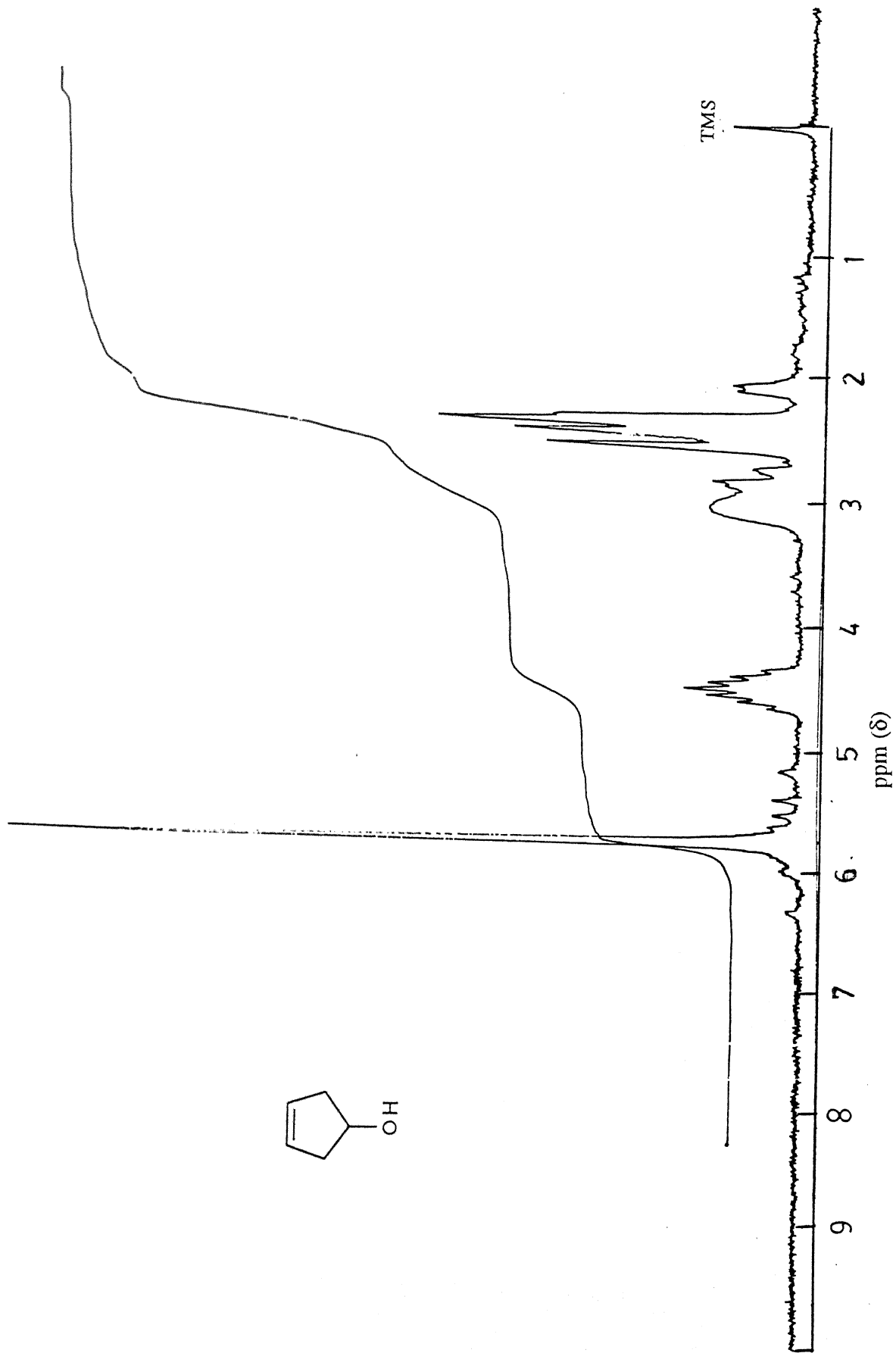


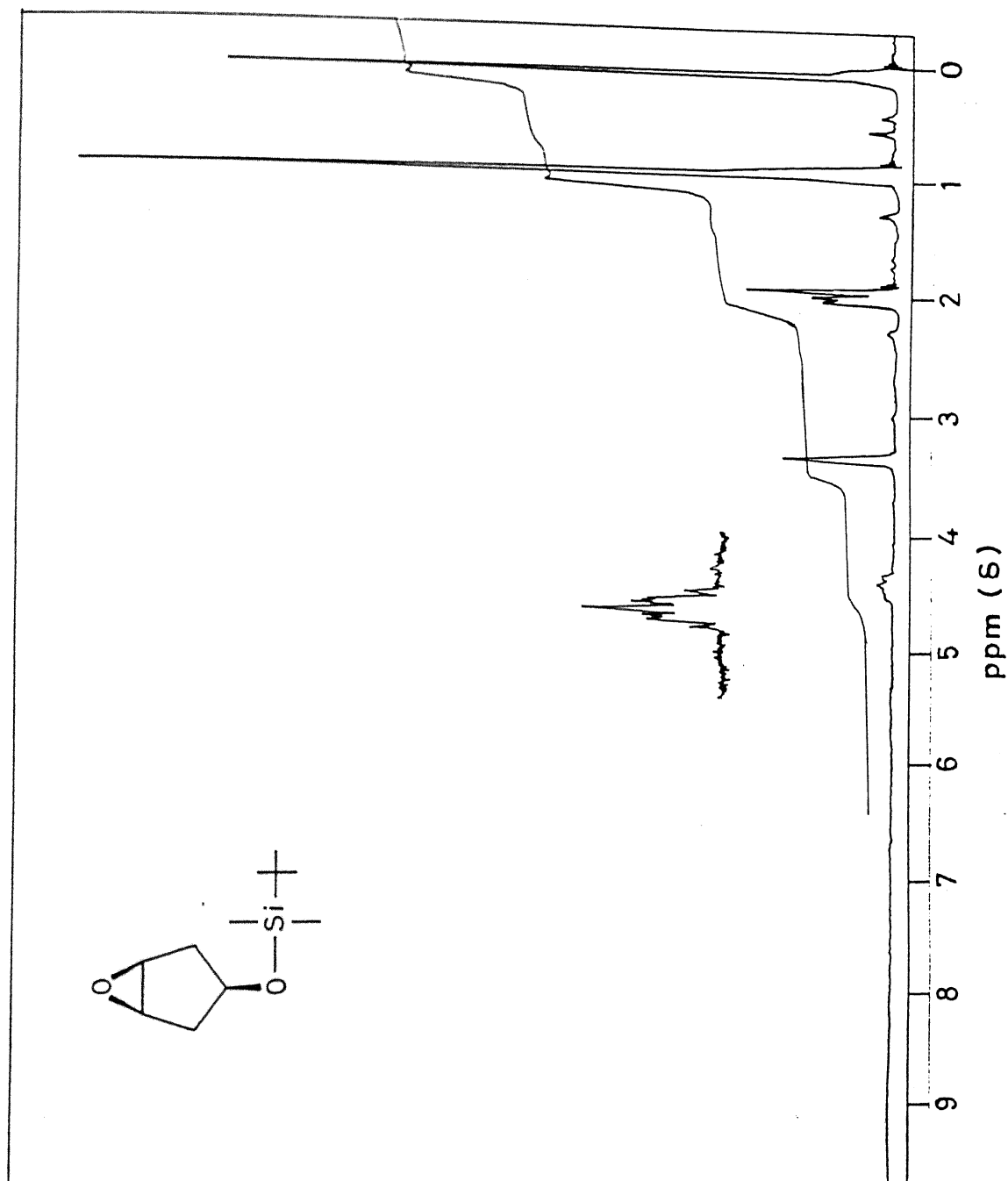
100 MHz ^{13}C NMR spectrum of (S)-1 in CDCl_3 .

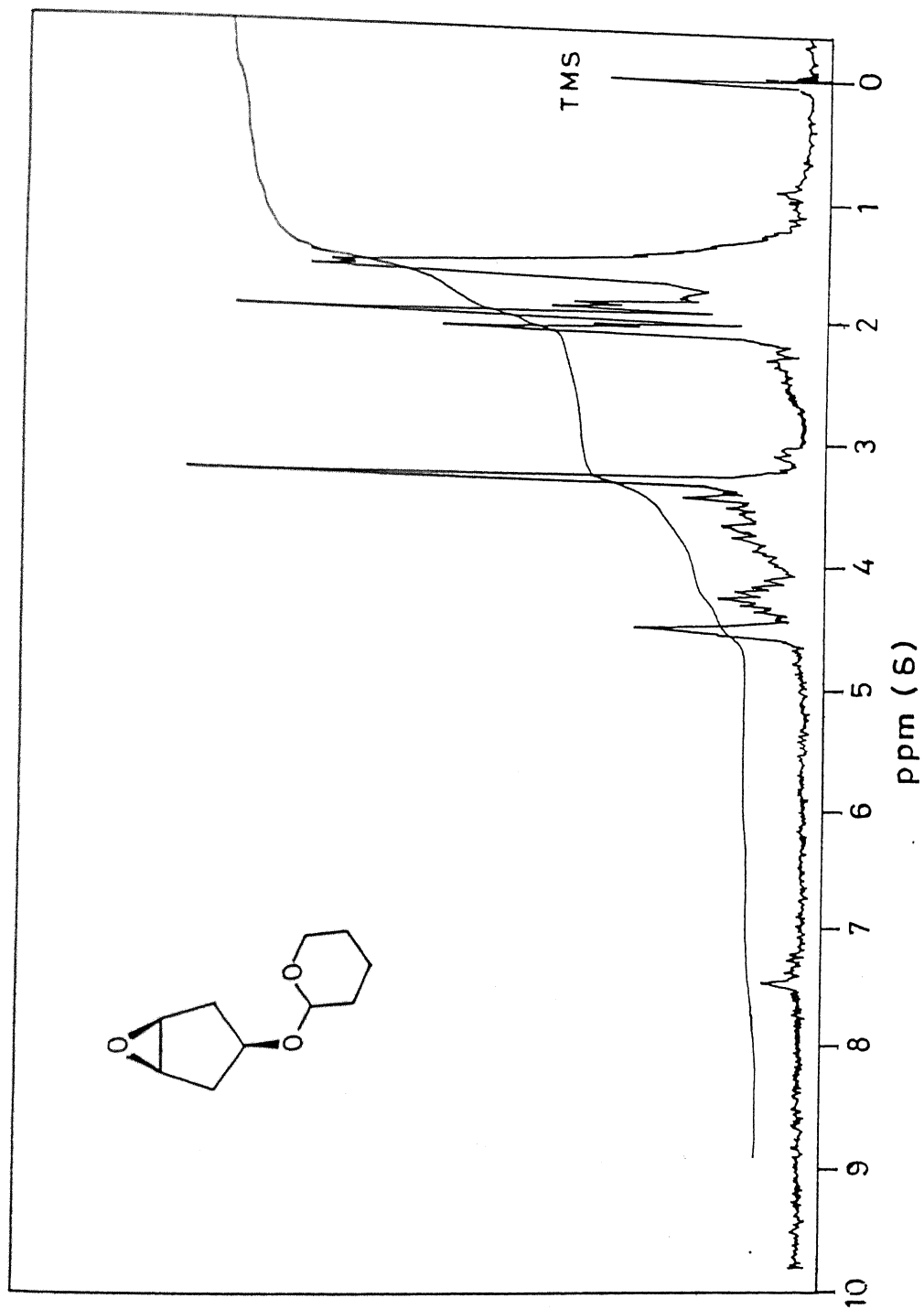
400 MHz ^1H NMR spectrum of **15** in CDCl_3 .

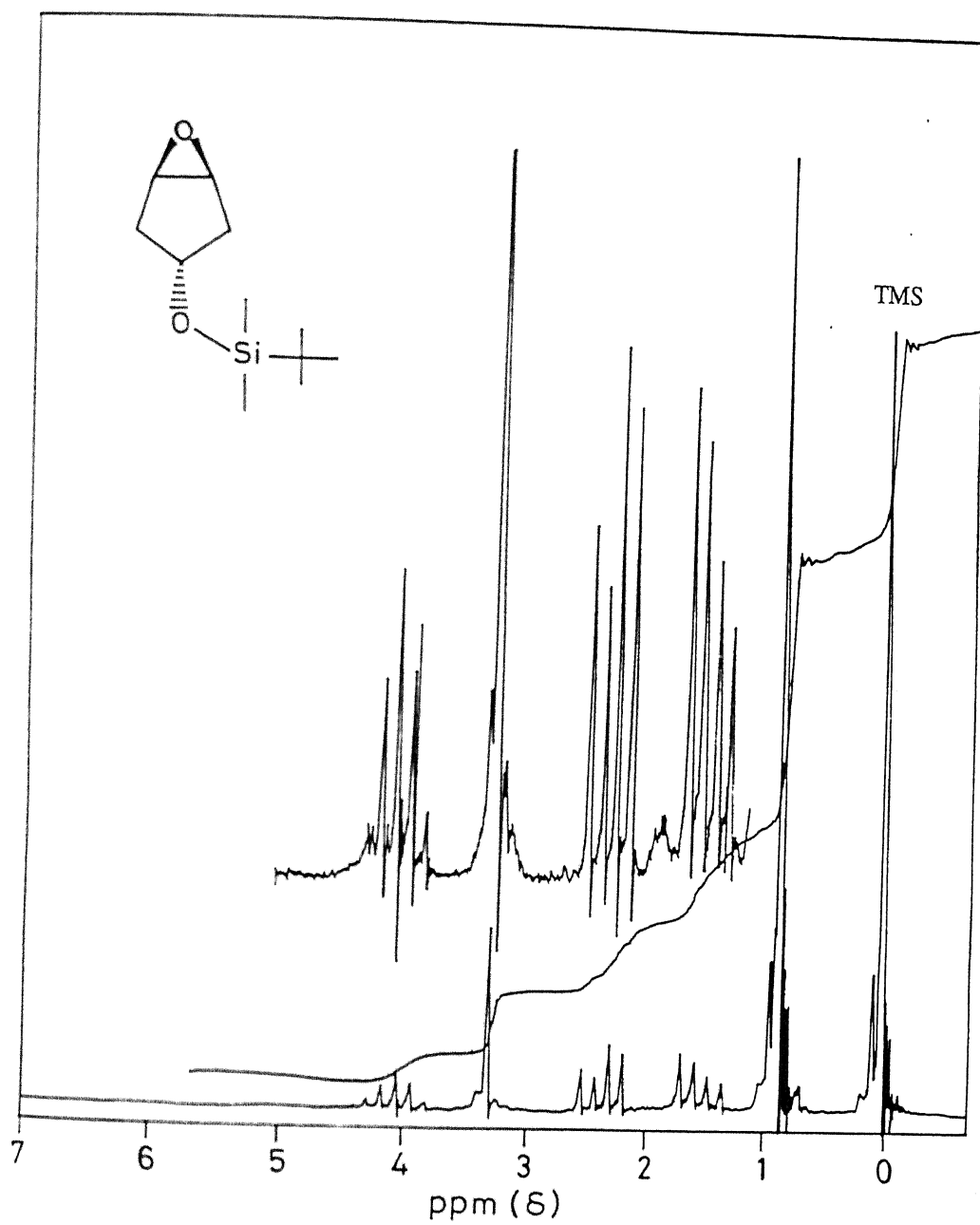


400 MHz ^1H NMR spectrum of **15** in CDCl_3 .

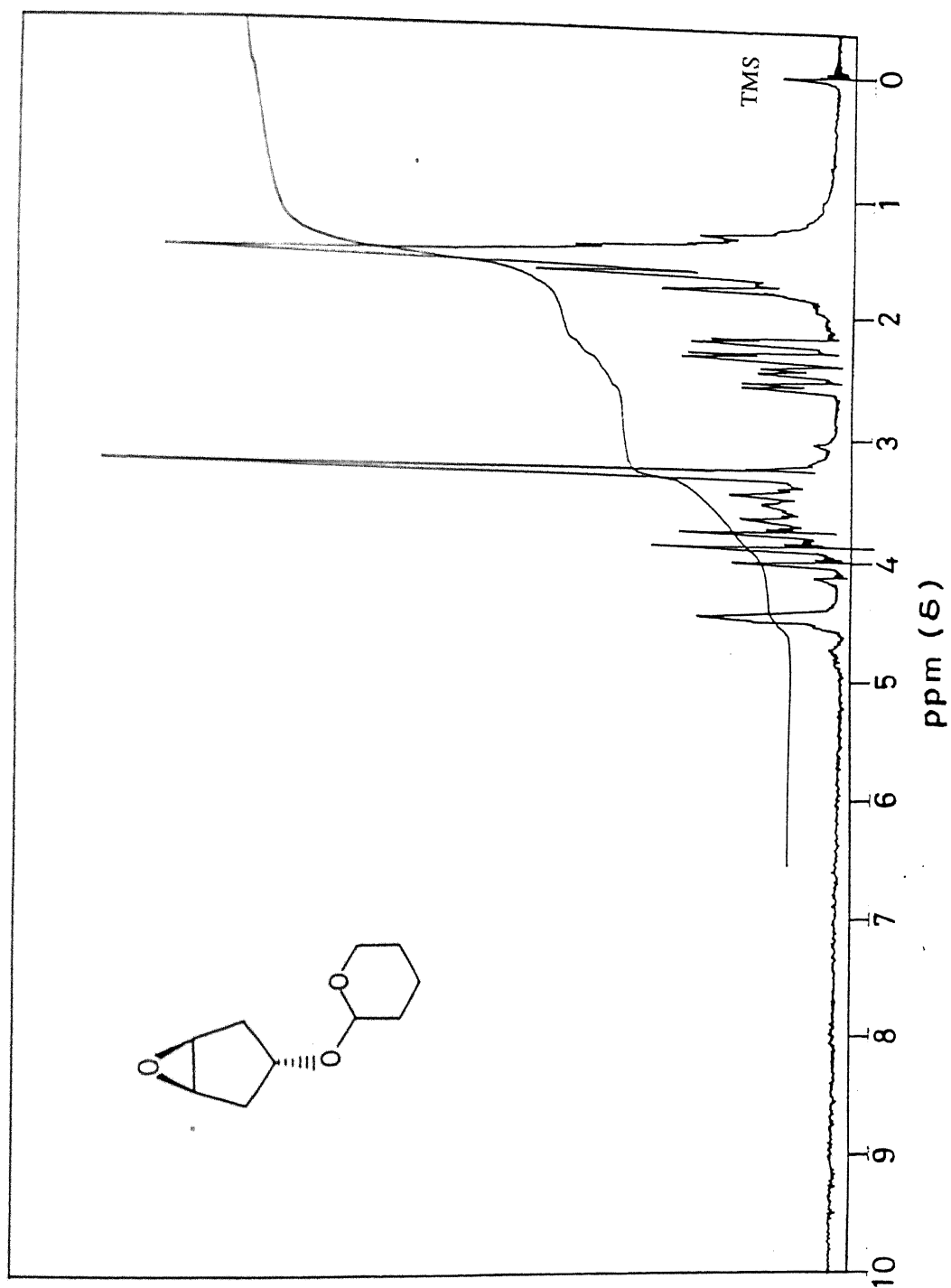
60 MHz ^1H NMR spectrum of **16** in CCl_4 .

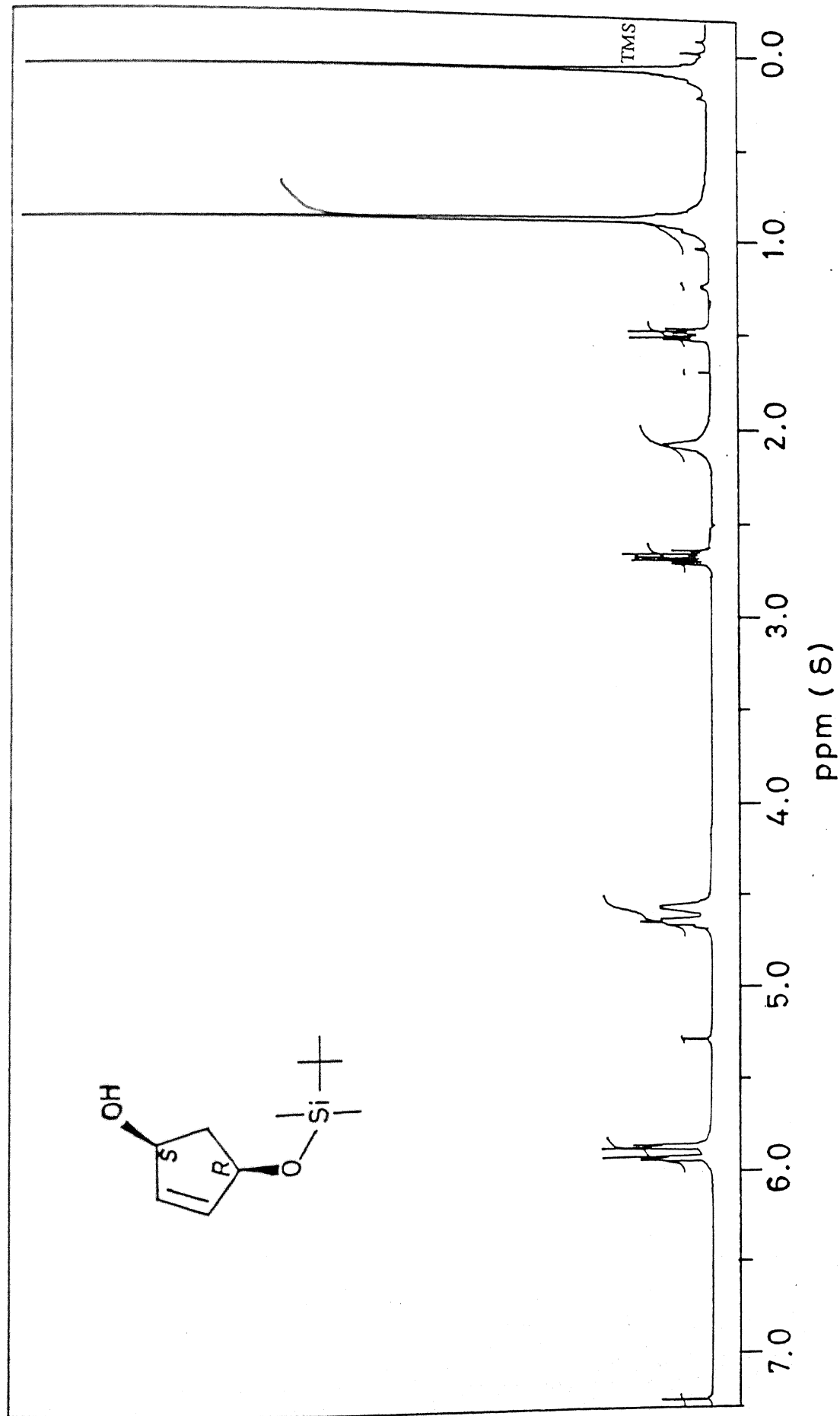
60 MHz ^1H NMR spectrum of **19a** in CCl_4 .

60 MHz ^1H NMR spectrum of **19b** in CCl_4 .

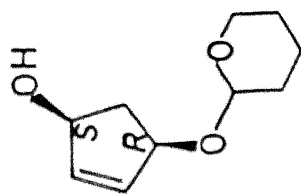


60 MHz ^1H NMR spectrum of **20a** in CCl_4 .

60 MHz ^1H NMR spectrum of **20b** in CCl_4 .



400 MHz ¹H NMR spectrum of (1S, 4R)-8a in CDCl₃.



TMS

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5.0

4.0

3.0

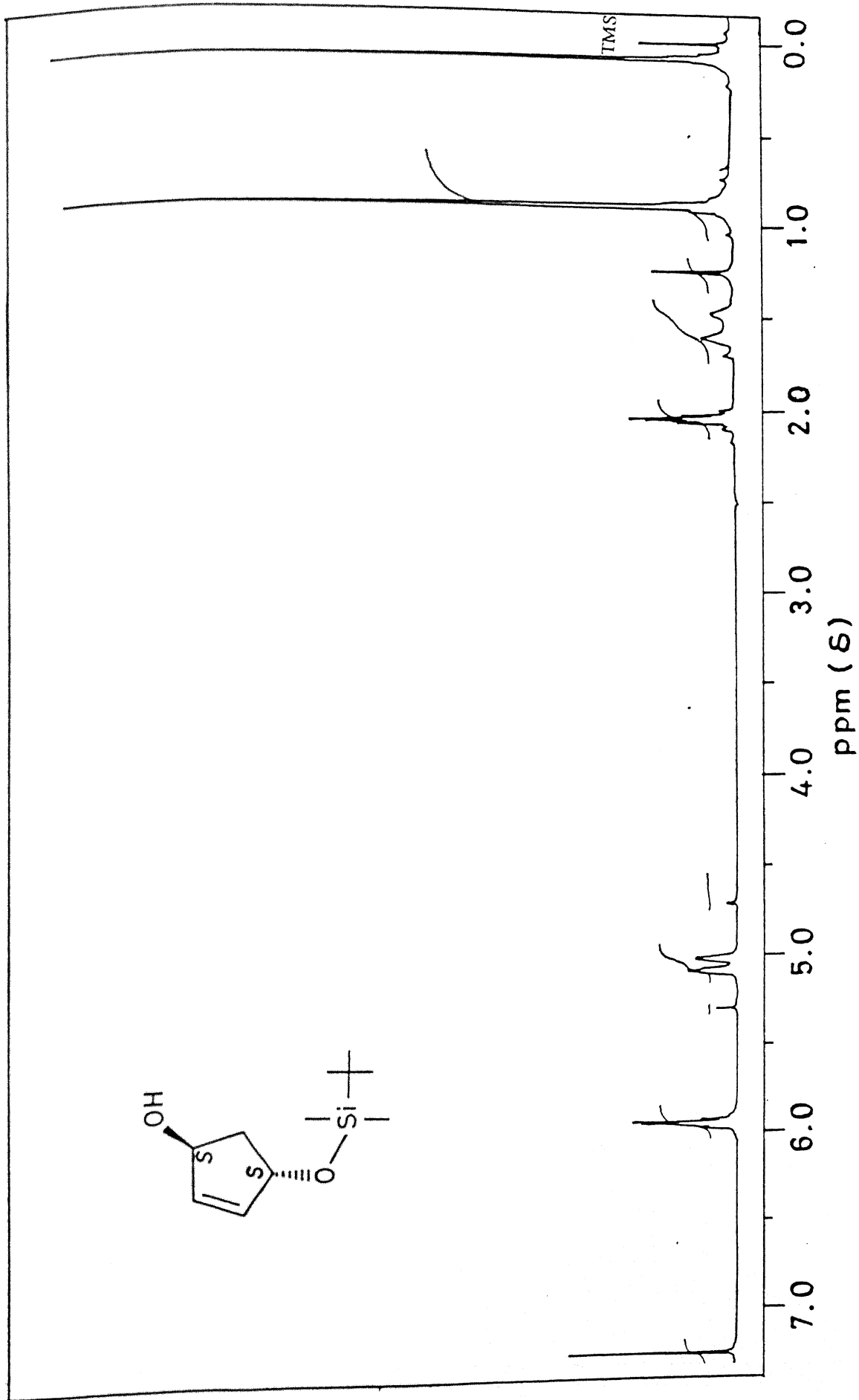
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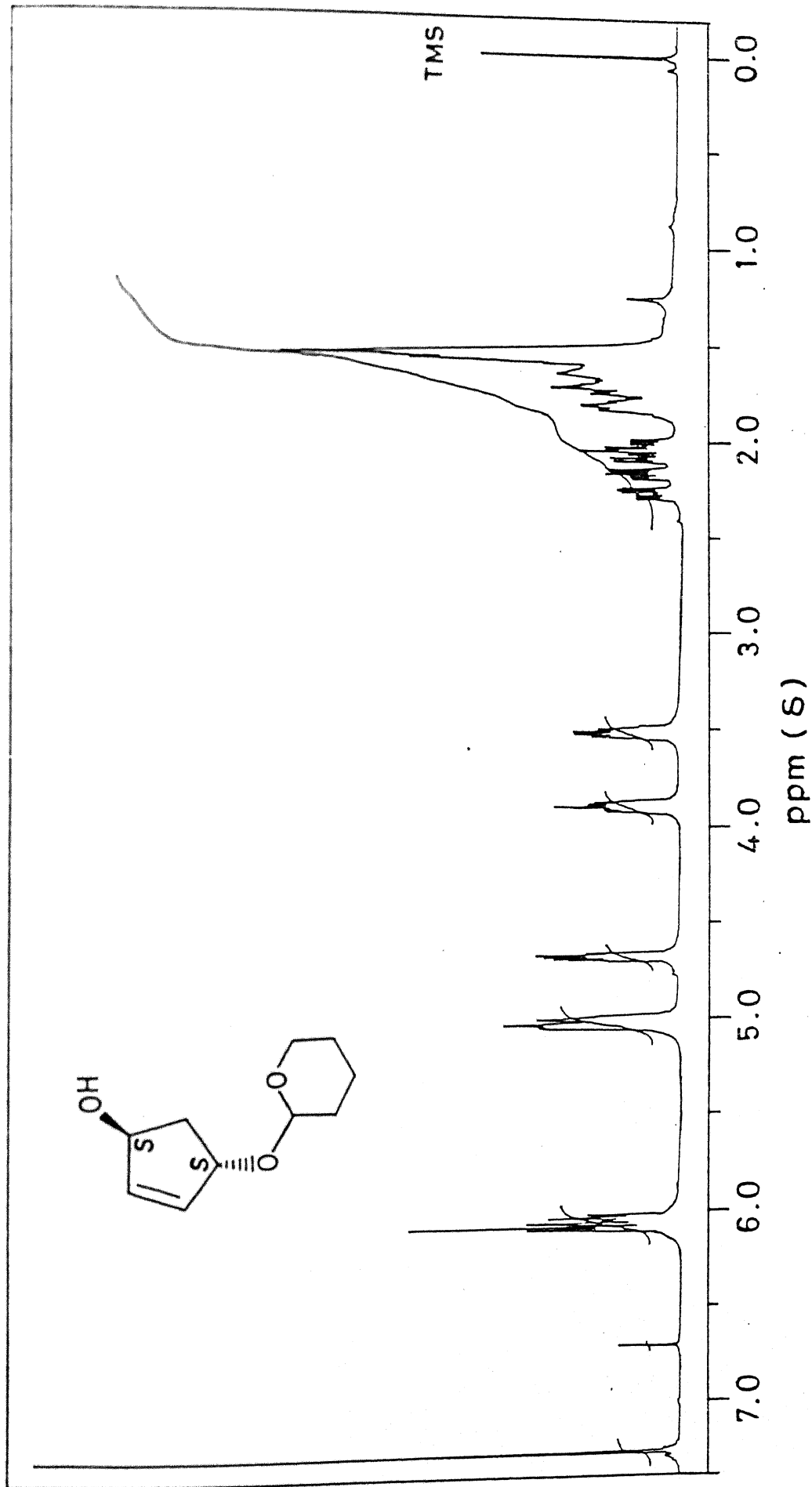
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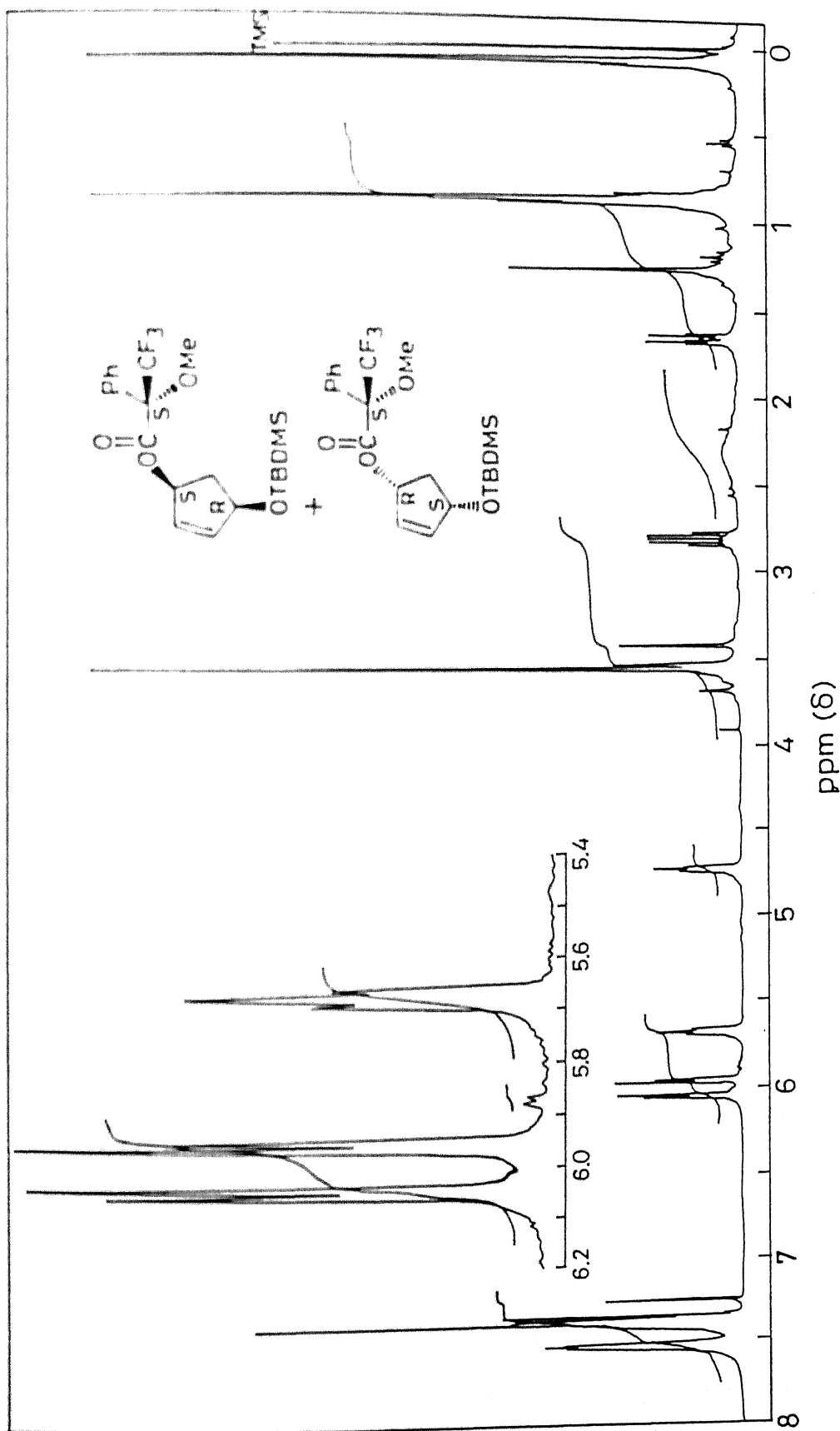
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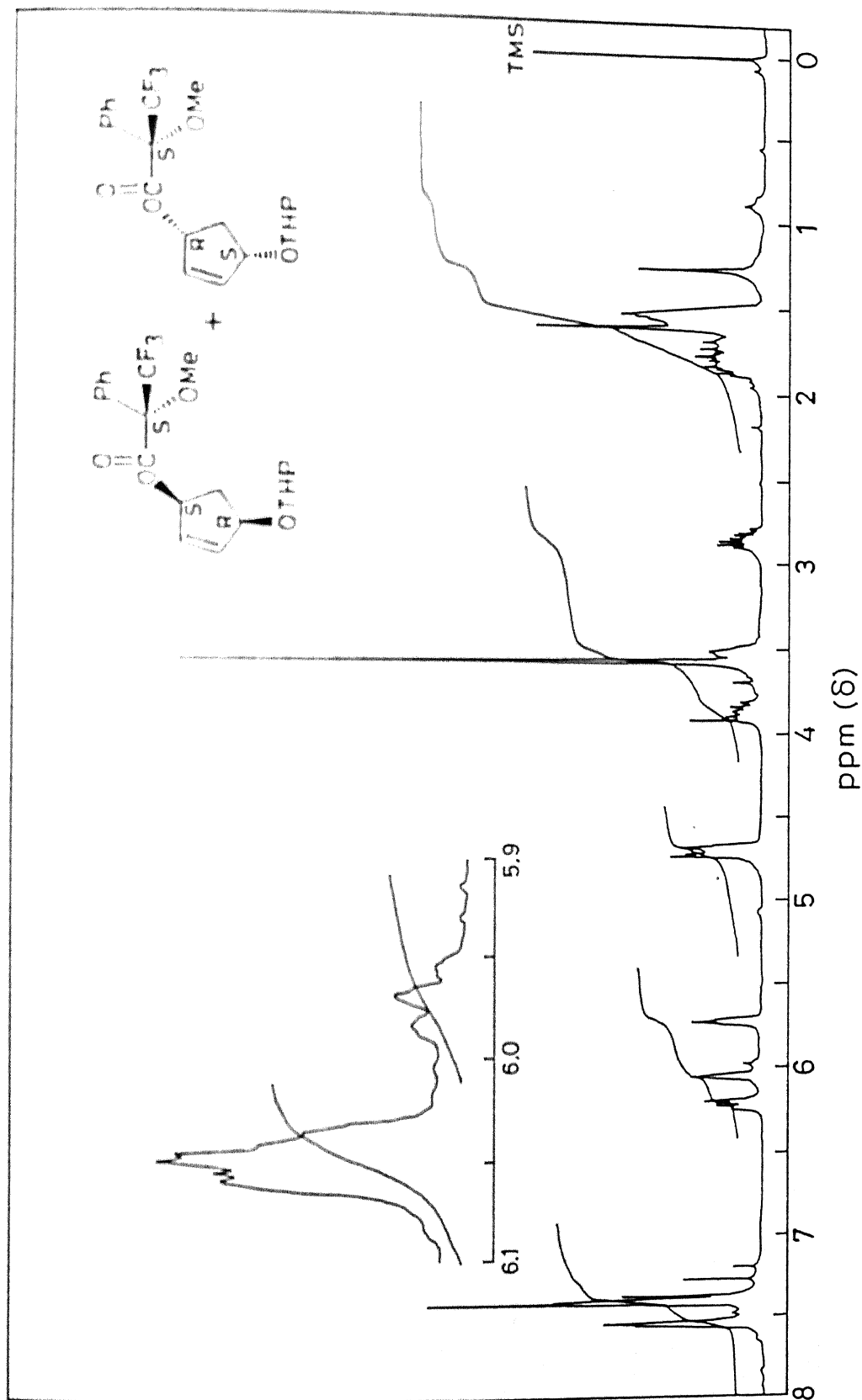


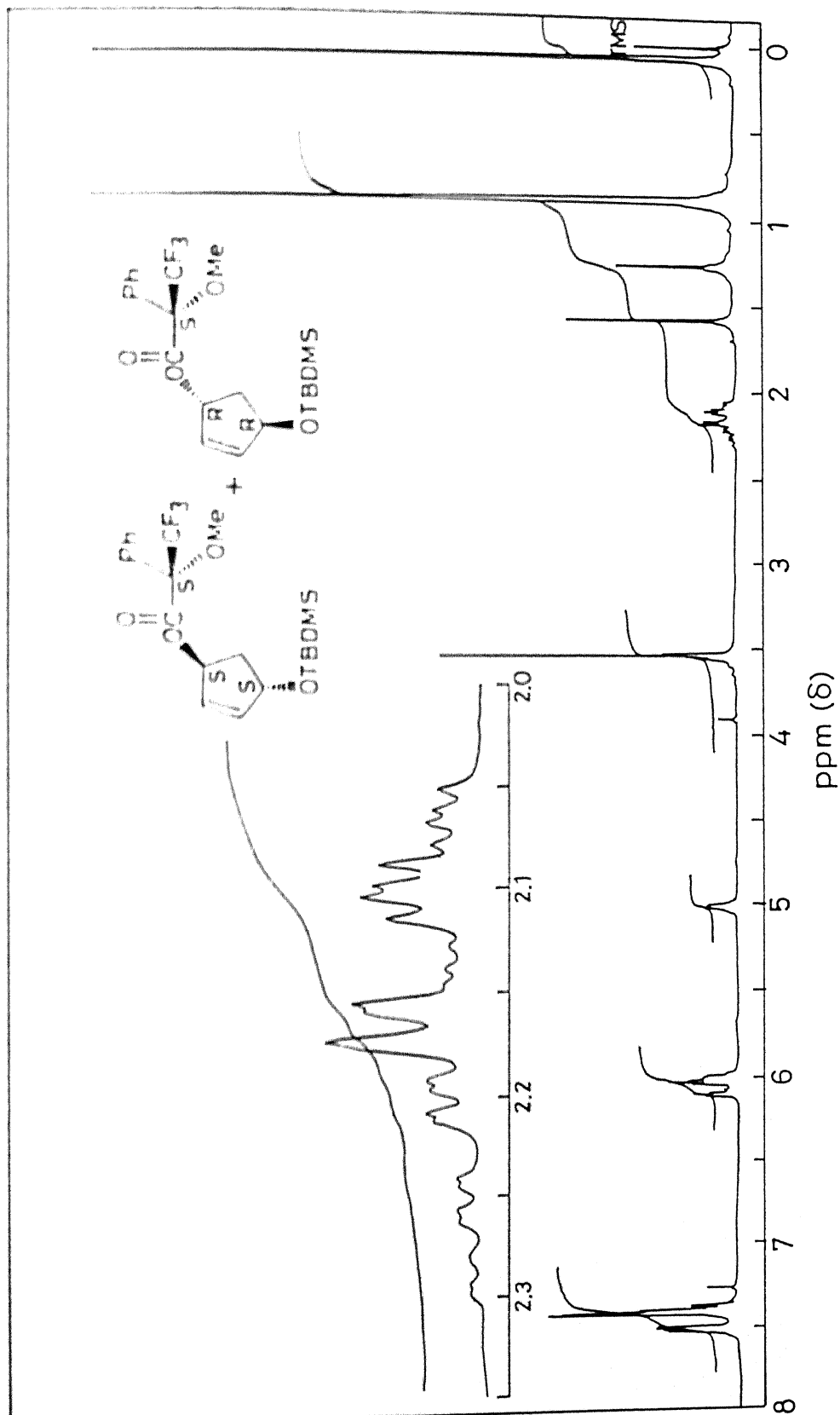
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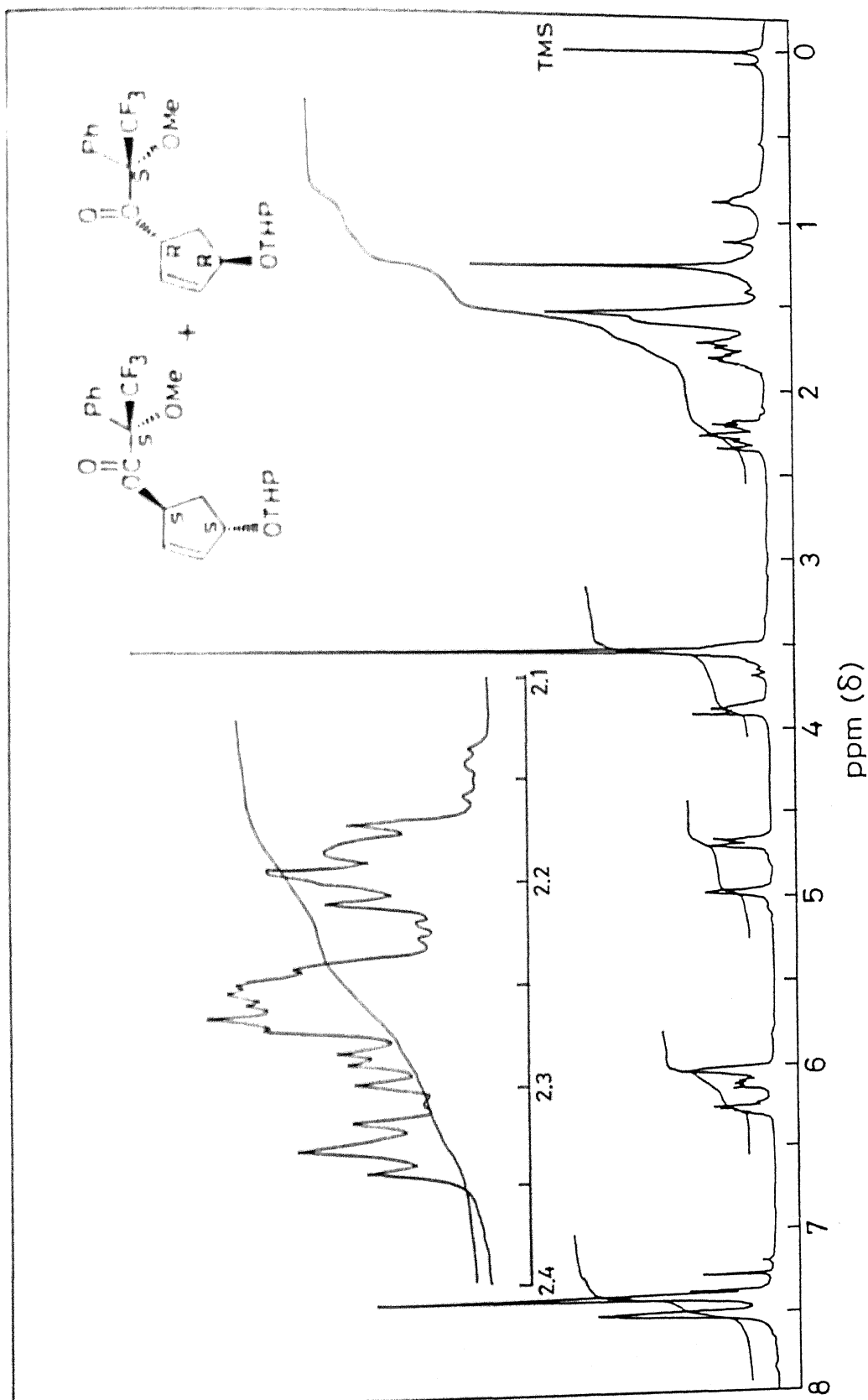


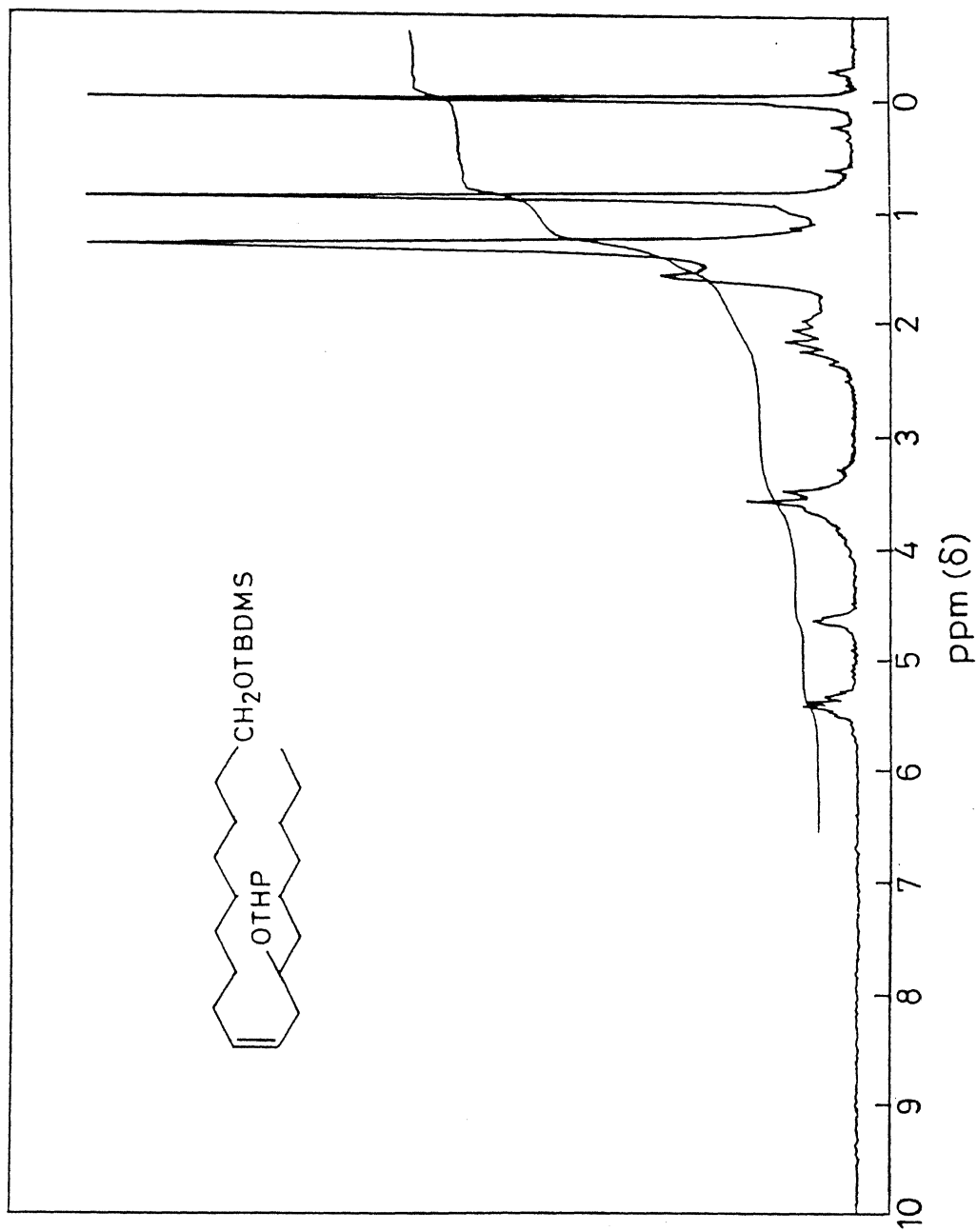
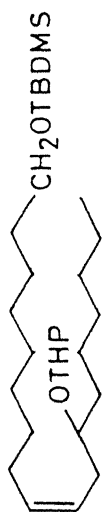
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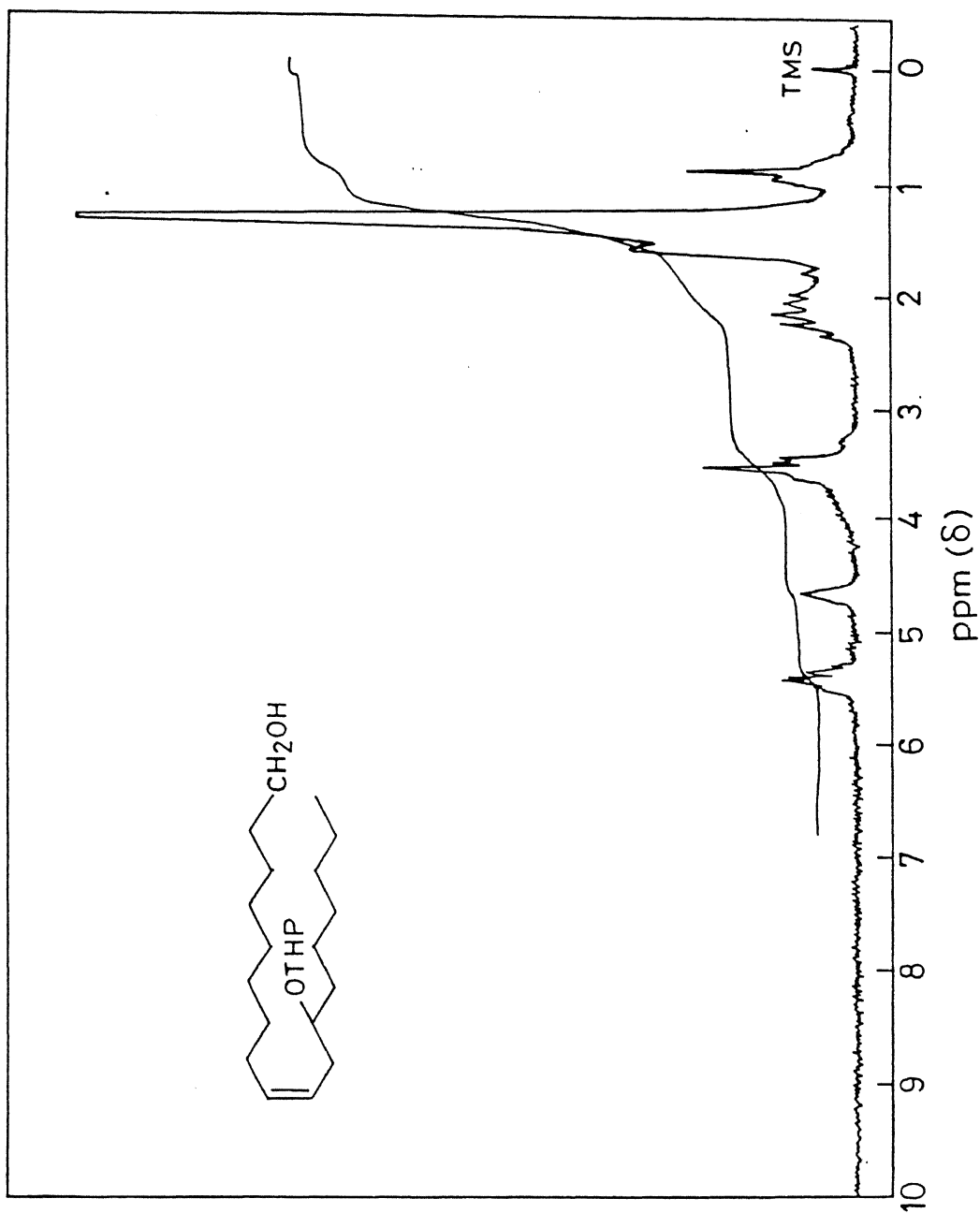
400 MHz ^1H NMR spectrum of Mosher esters of **8b** in CDCl_3 .



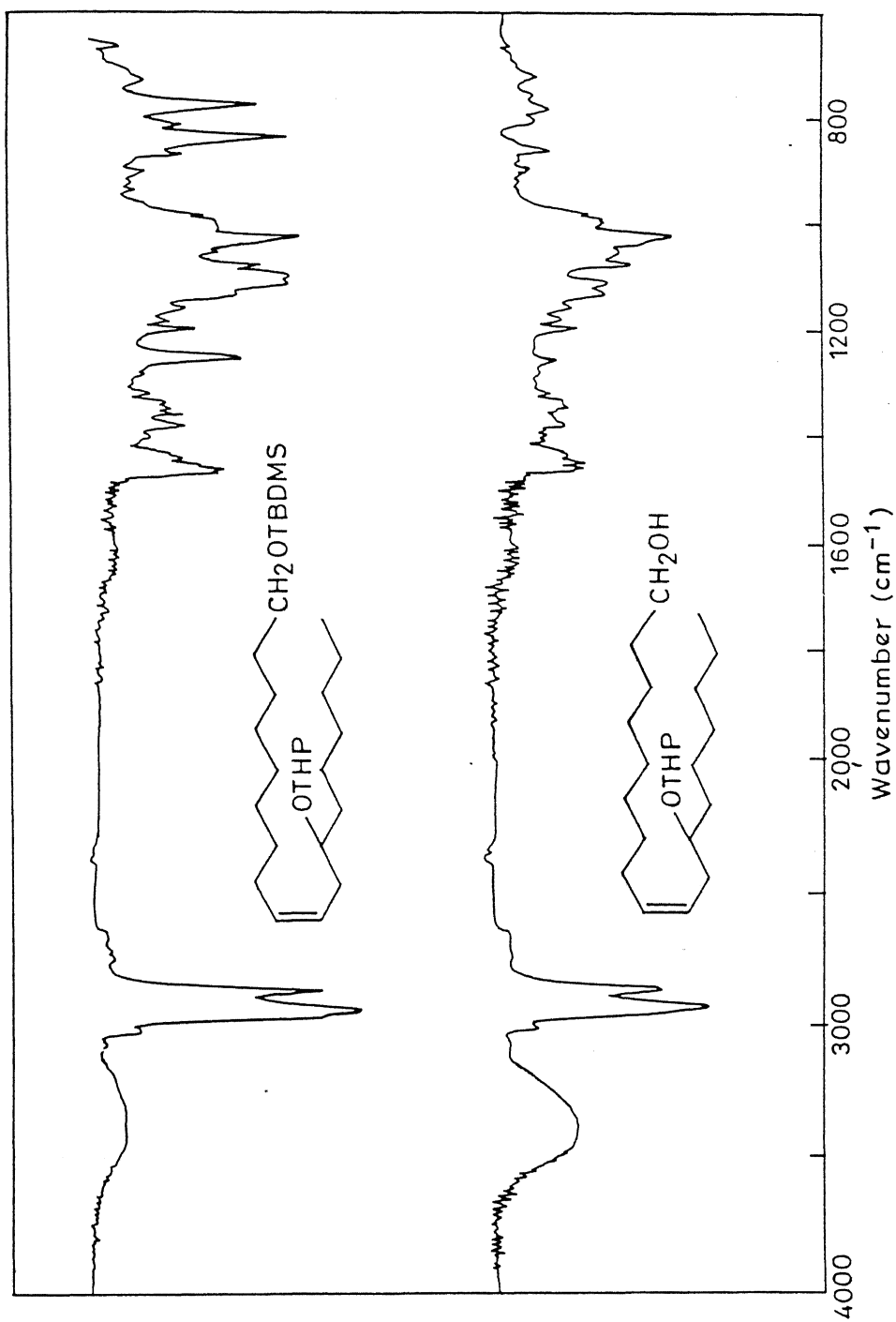
400 MHz ^1H NMR spectrum of Mosher ester of **22b** in CDCl_3 .

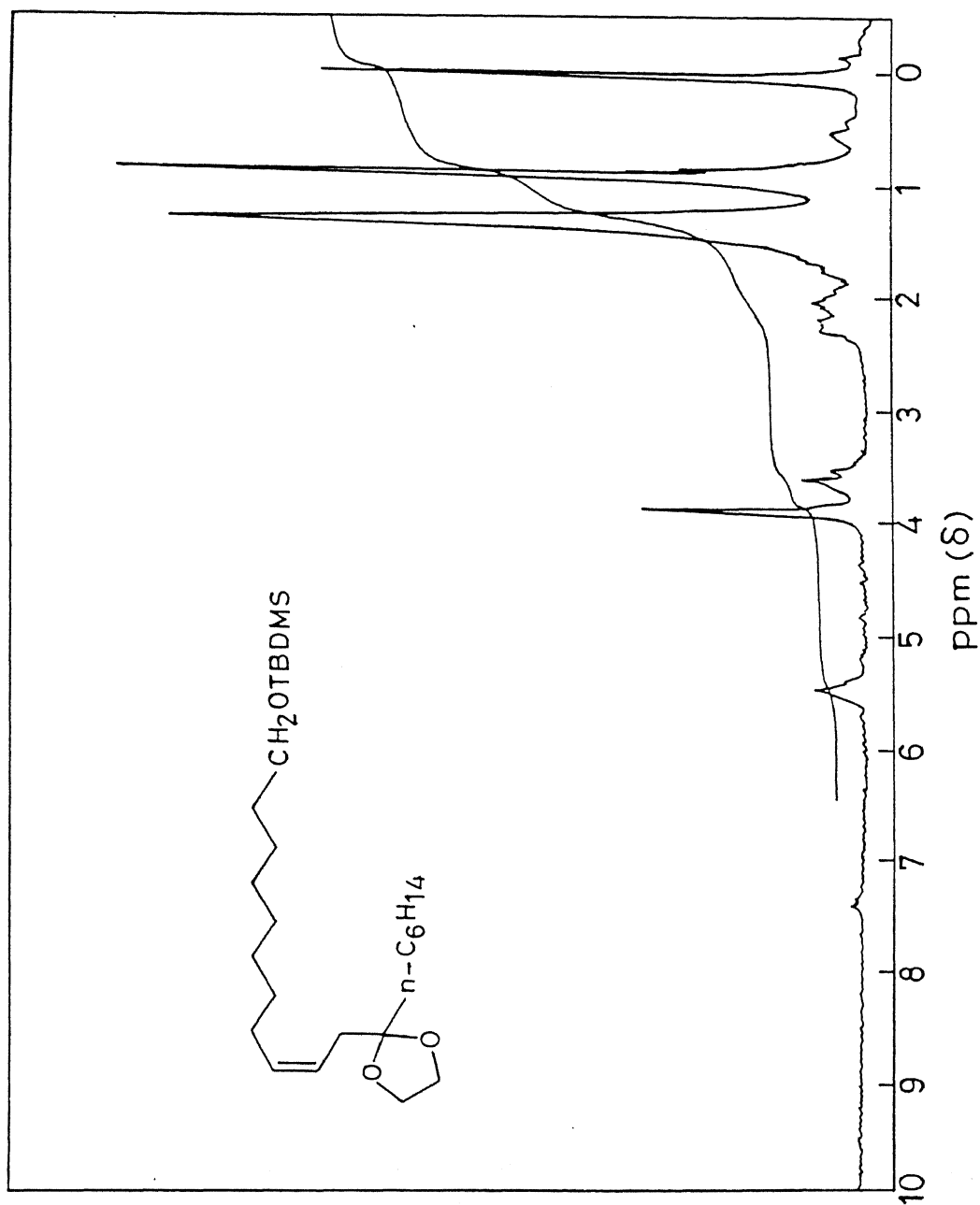


60 MHz ¹H NMR spectrum of **42** in CCl₄.

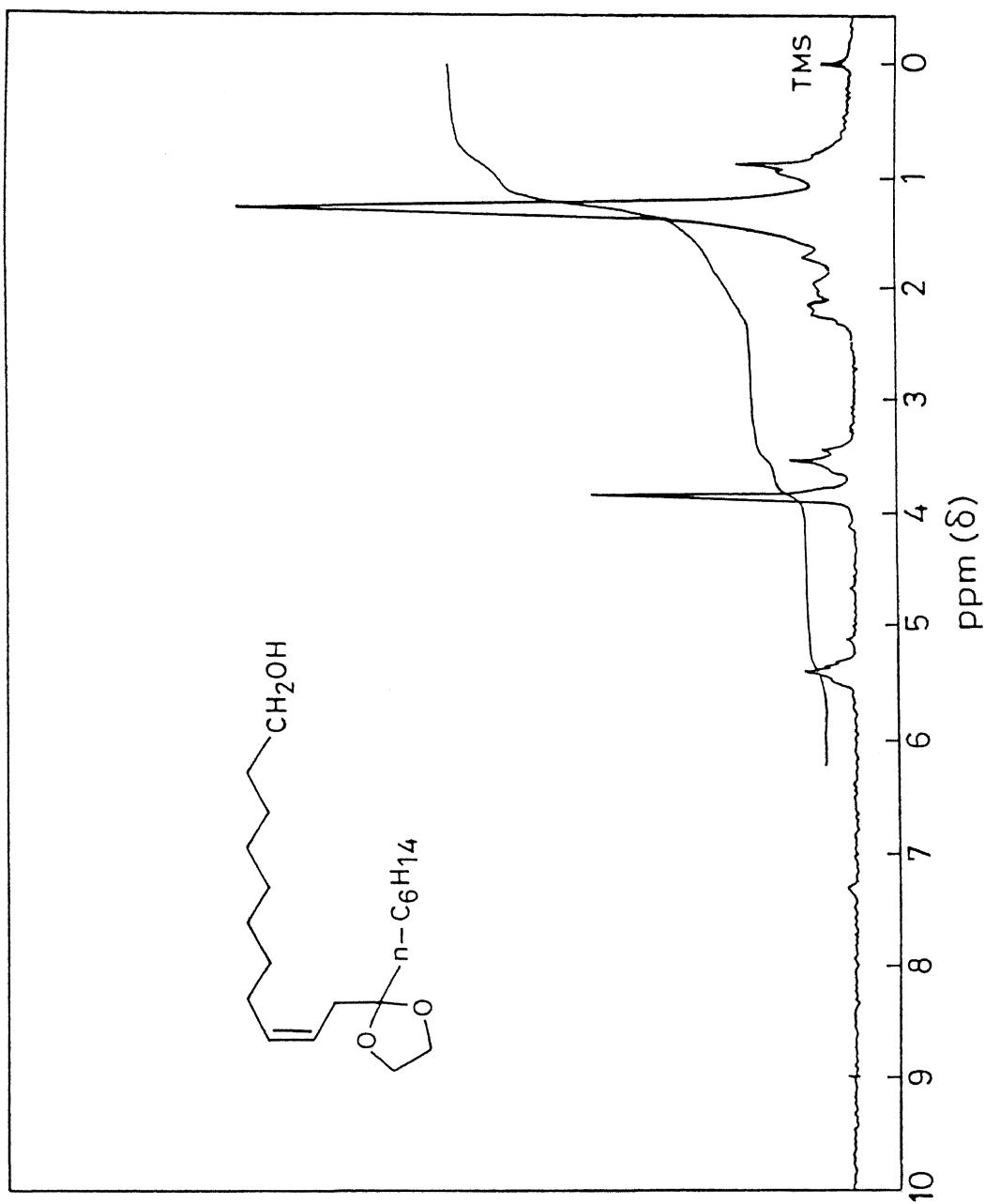


60 MHz ^1H NMR spectrum of **41** in CCl_4 .

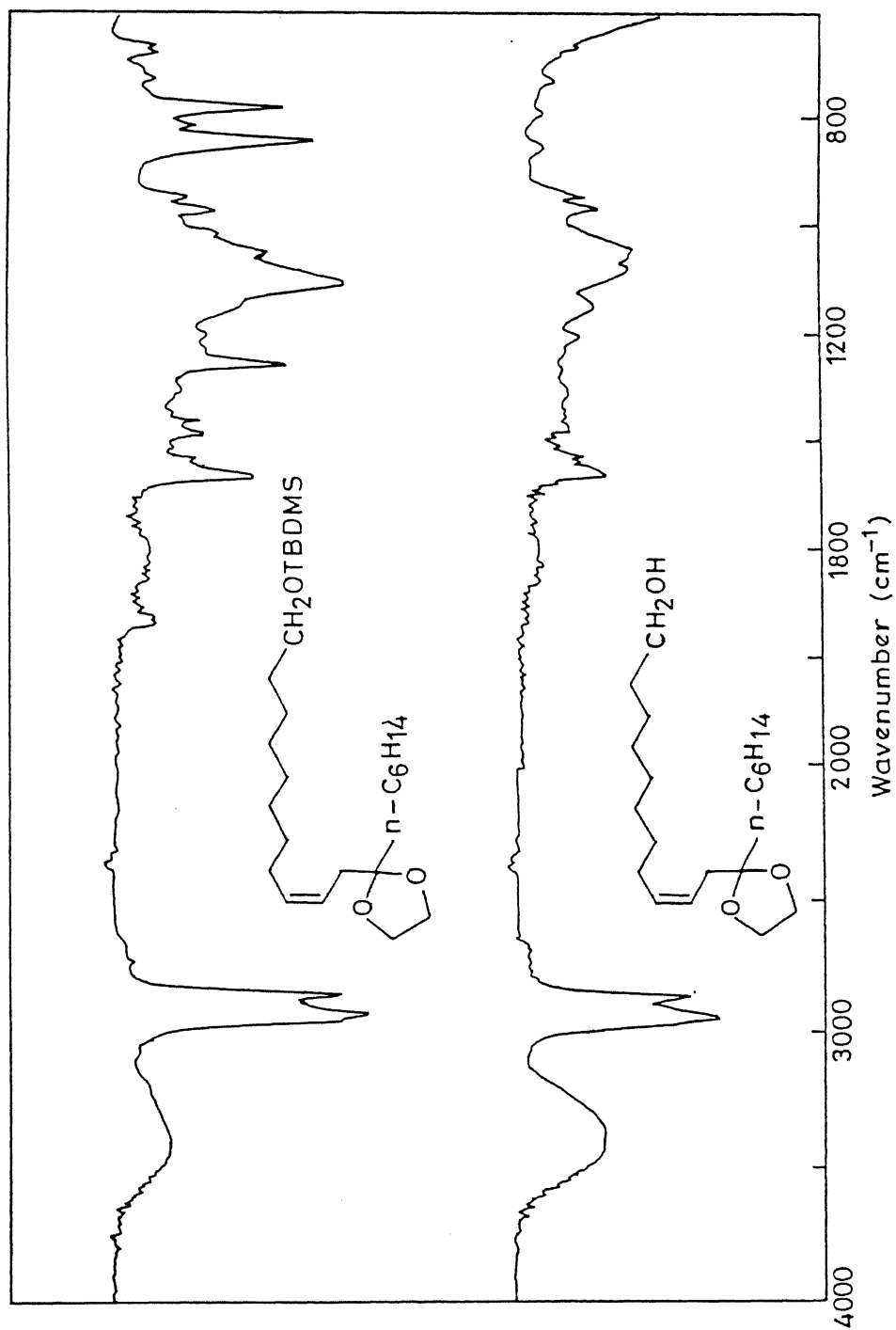


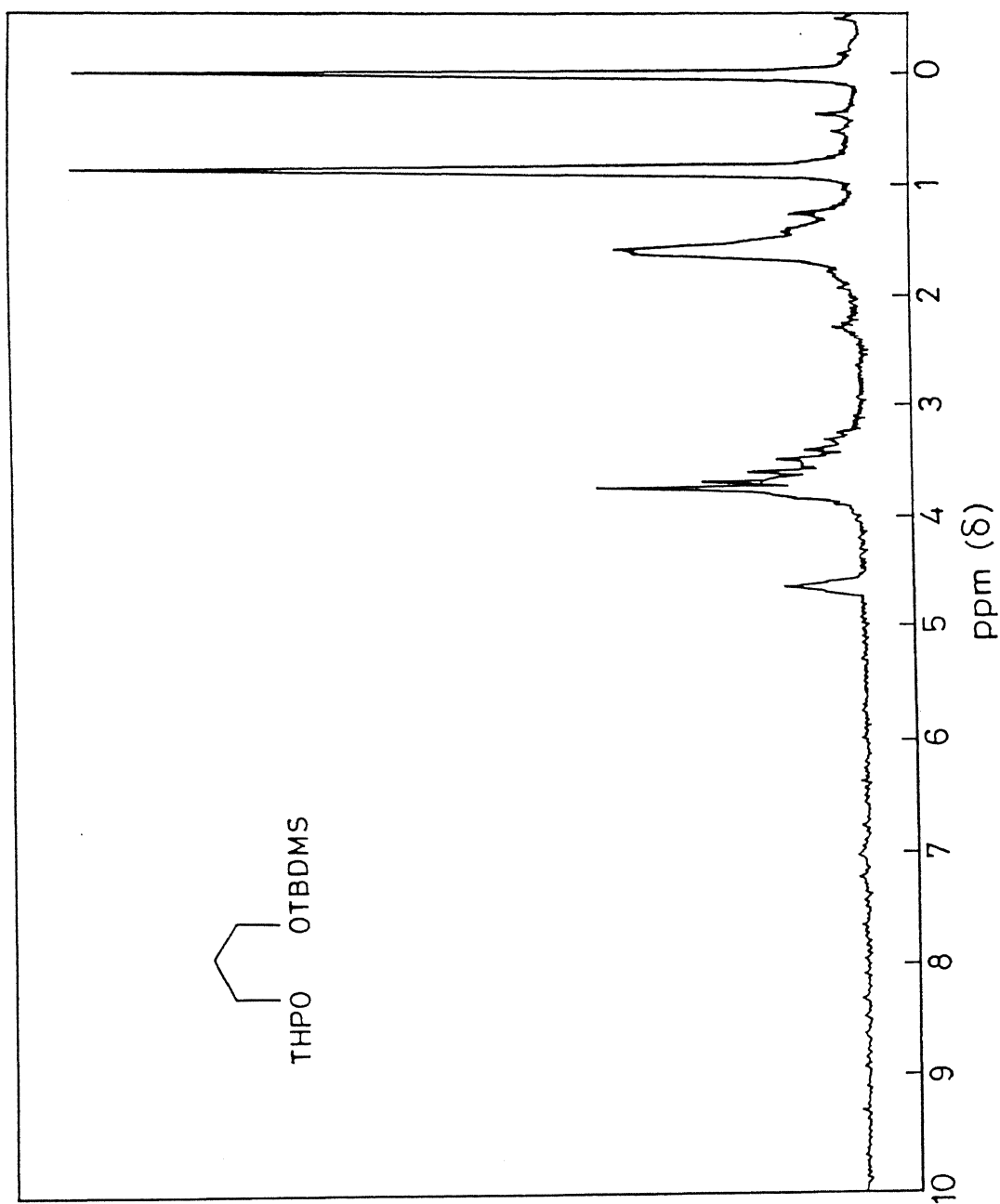


60 MHz ^1H NMR spectrum of **46** in CCl_4 .

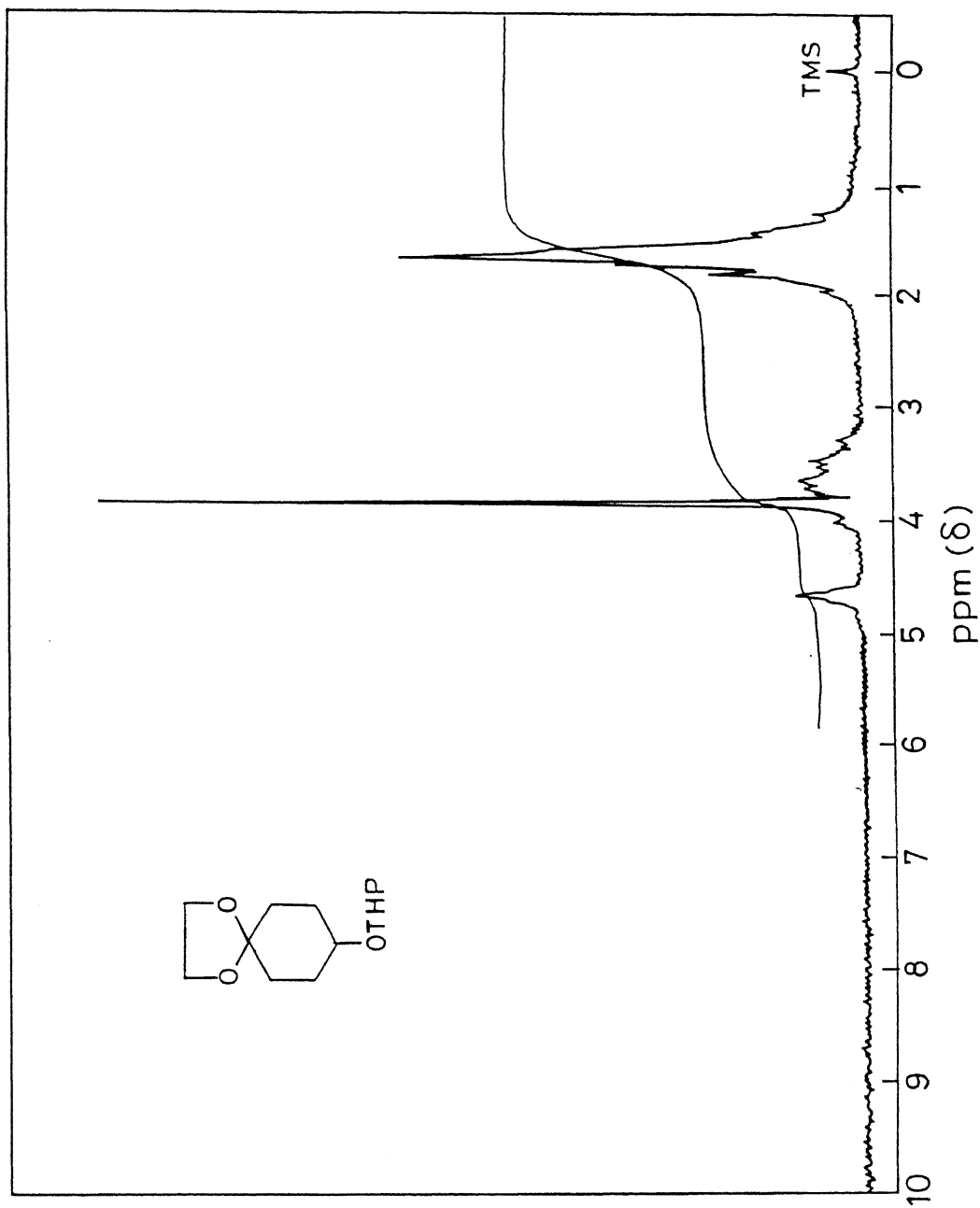


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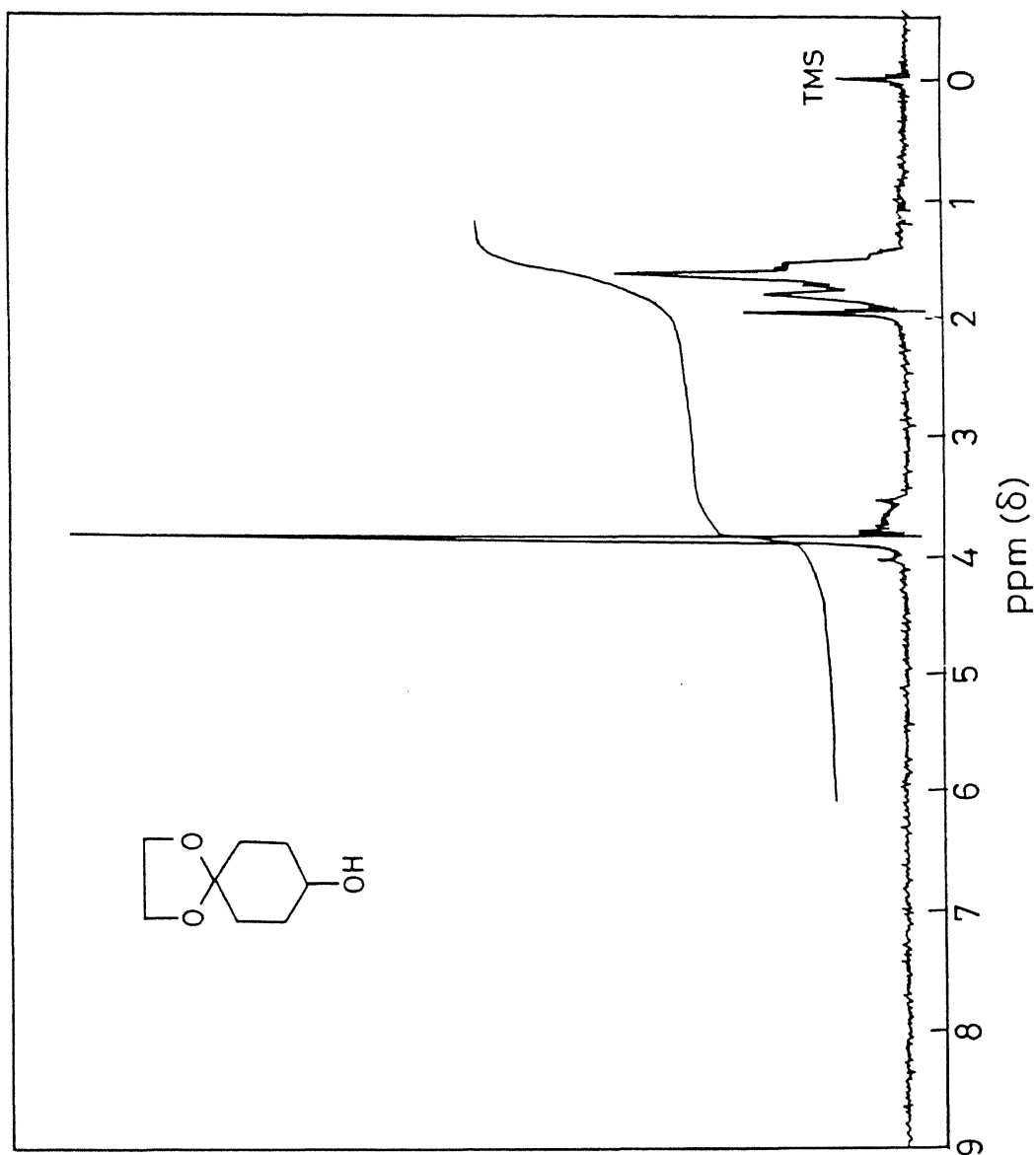


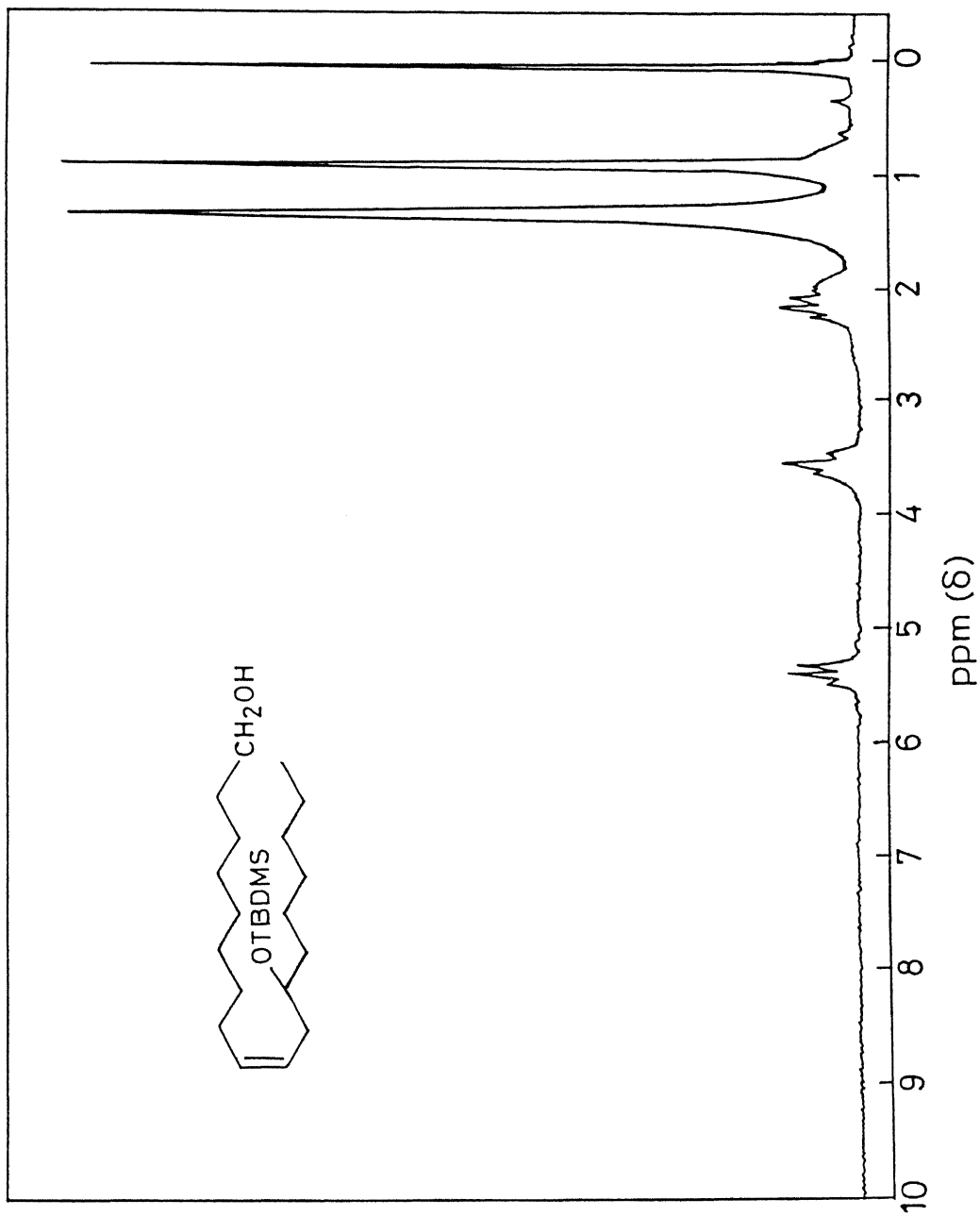


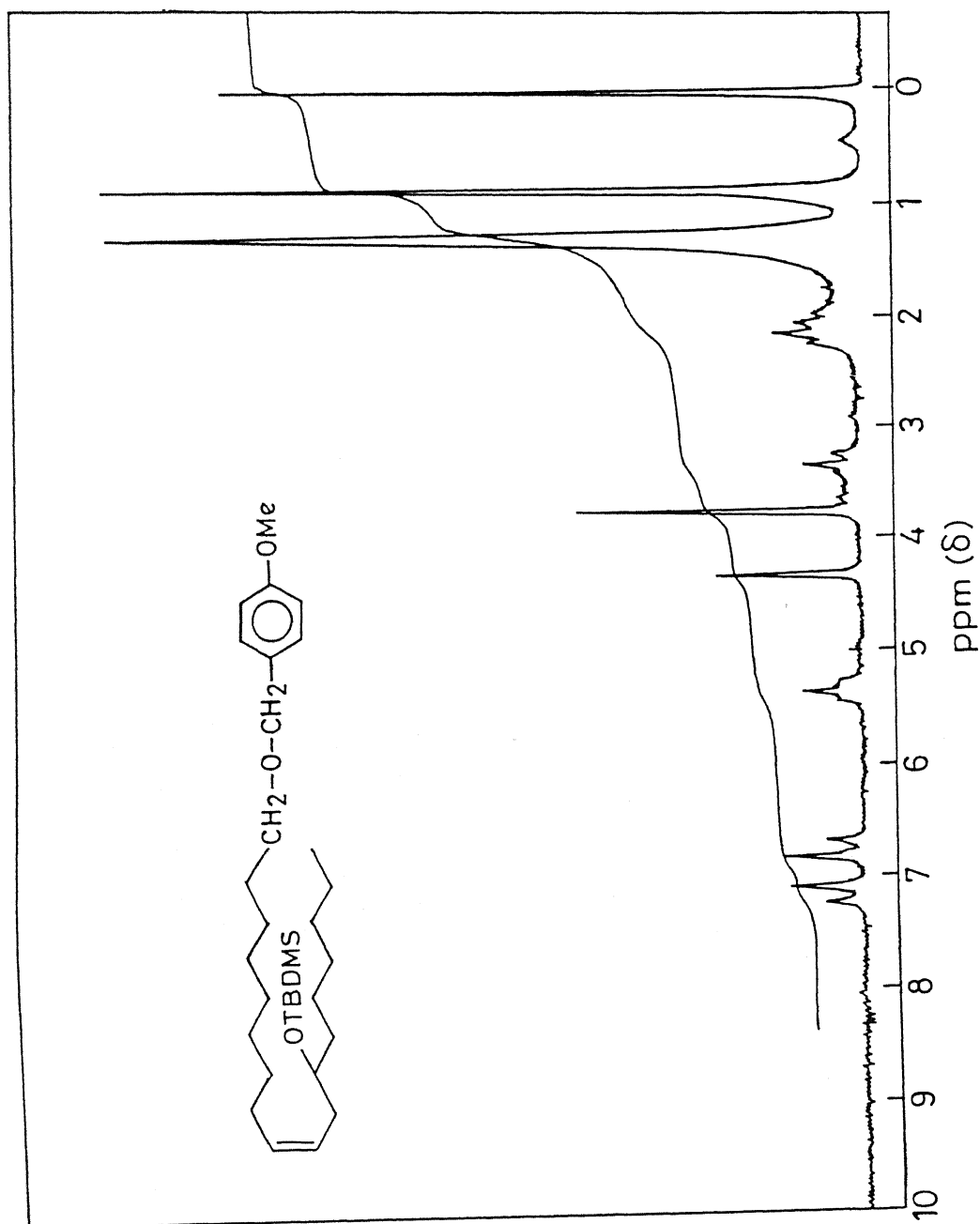
60 MHz ^1H NMR spectrum of **48** in CCl_4 .



60 MHz ^1H NMR spectrum of **51** in CCl_4 .



60 MHz ^1H NMR spectrum of **52** in CCl_4 .

60 MHz ^1H NMR spectrum of **53** in CCl_4 .

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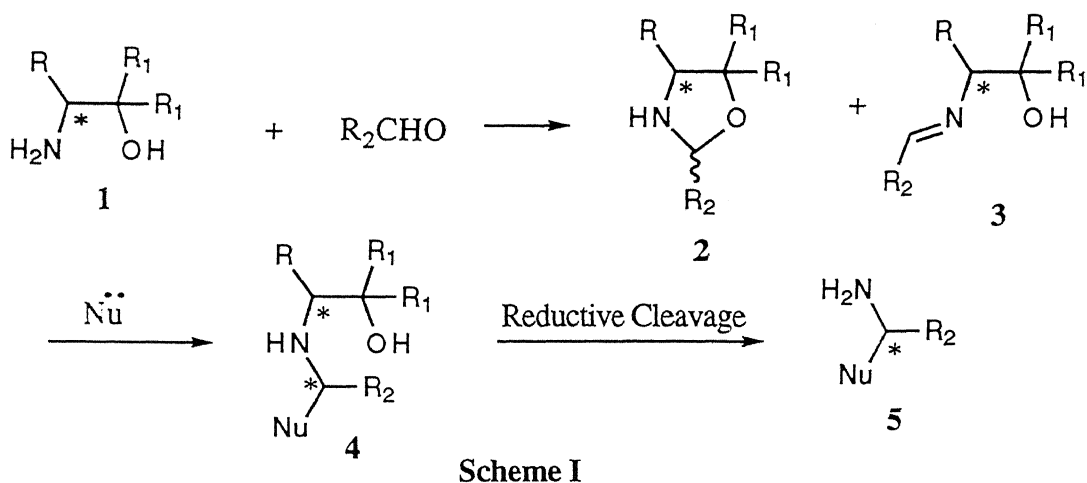
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 39. The pH of CAN solution in methanol at 0 °C indicates that the solution is acidic (mild). After few hours (usually 5-6 h) the colour of the solution turns colourless (pH 1-2).
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**AN APPROACH TOWARDS SYNTHESIS OF
- ENANTIOPURE AMINES**

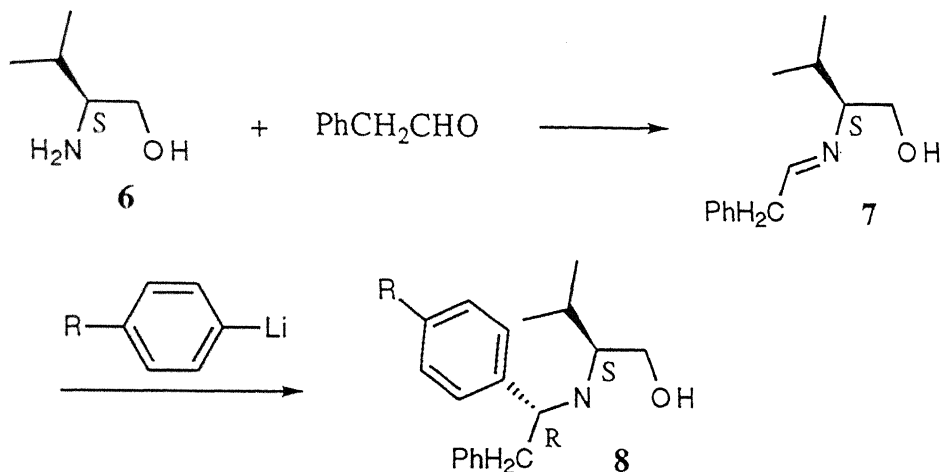
Enantiopure amines are very useful in synthetic organic chemistry. One of the approaches towards the synthesis of chiral amines is based on auxiliary (Scheme I). In this approach, an aminoalcohols of the type **1** reacts with an aldehyde to form oxazolidine **2** and/or imine **3**. The addition of nucleophile to the carbon nitrogen double bond of imine and/or oxazolidine carbon leads to the formation of addition adduct **4**.¹ The susceptibility of carbon-oxygen and nitrogen-arylalkyl bonds within these addition products to reductive cleavage contributes to their values for the asymmetric synthesis of amines **5** (Scheme I). This plausible synthesis of optically active amines has been studied a lot and exploited for last several years.



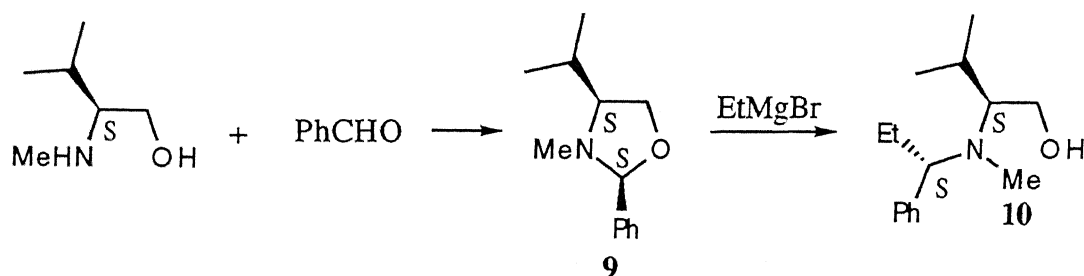
Scheme I

In 1982, Takahashi *et al.* described the synthesis of asymmetric α -substituted phenethylamines.² The condensation of *S*-valinol **6** with phenylacetaldehyde gave solely the *E* isomer of (*S*)-(+)-*N*-(2-hydroxy-1-isopropylethyl)phenylethylideneamine **7**. This imine on treatment with benzylmagnesium chloride or aryllithium gave chiral amine **8** (Scheme II) in more than 98% diastereomeric excess. A mechanism involving chelation mediated delivery of the organometallic reagent has been suggested.¹

Takahashi *et al.* extended the work³ to the formation of chiral oxazolidine **9** using (*S*)-*N*-methylvalinol and studied the action of Grignard reagent on these compounds (Scheme III). They obtained amine **10** as the major diastereomer (diastereomeric ratio = 9:1). The magnesium atom of the Grignard reagent coordinated to the lone pair of the oxygen from the less hindered side and then the alkyl anion attacked the α -carbon from the same side to give the major product.

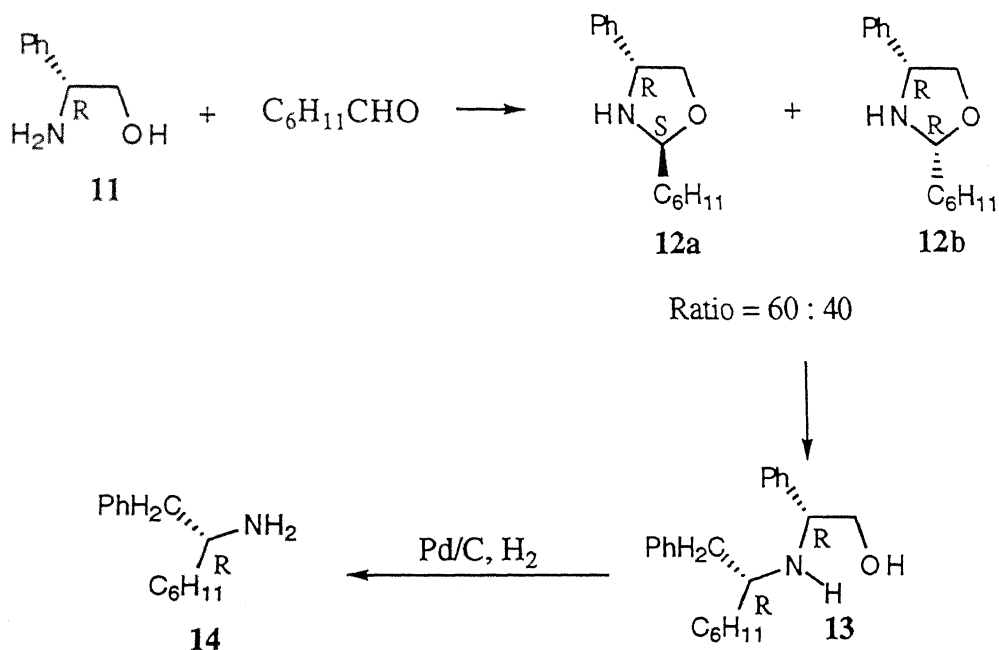


Scheme II



Scheme III

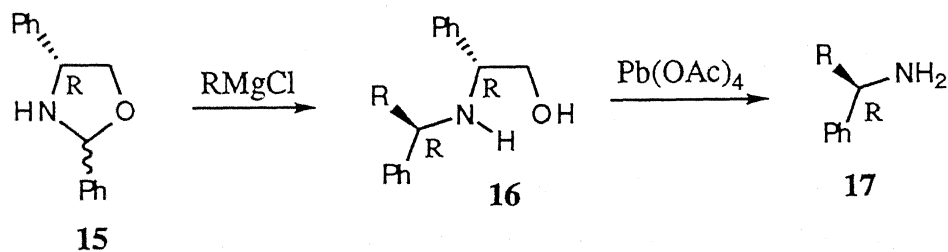
Takahashi and coworkers⁴ also used (*S*)-*O*-methoxy valinol for the synthesis of chiral amines. They did similar studies⁵ with chiral *N*-methyl-4-phenyl-1,3-oxazolidines derived from phenylglycinol. They also showed^{6a} that unsubstituted (*R*)-phenylglycinol **11** gave a diastereomeric mixture (60:40) of the two oxazolidines **12a** and **12b** on reaction with cyclohexanecarbaldehyde. However this diastereomeric mixture, when was reacted with benzylmagnesium chloride, gave (1*R*,1'*R*)-1-cyclohexyl-*N*-2'-hydroxy-1'-phenylethyl-2-phenylethylamine **13** as an optically active single diastereomer. This reaction involved attack by one Grignard reagent molecule on the oxygen of **12a** and **12b** followed by the *cis*-imine rearrangement to the *trans*-isomer. Then another Grignard reagent molecule attacked from the *Re* face at the carbon-nitrogen double bond. The compound **13** was hydrogenolyzed with a Pd-carbon catalyst in acetic acid solution to give (*R*)-1-cyclohexyl-2-phenylethylamine **14** (Scheme



Scheme IV

Takahashi *et al.*^{6b}, carried on the reactions of chiral N-methyl-4-phenyl-1,3-oxazolidine with Grignard reagent and organotitanium reagent. The sense of asymmetric induction was found to be opposite in the two cases. The chiral oxazolidines derived from N-substituted (*R*)-phenylglycinol and *p*-bromobenzaldehyde were also studied in detail.⁷

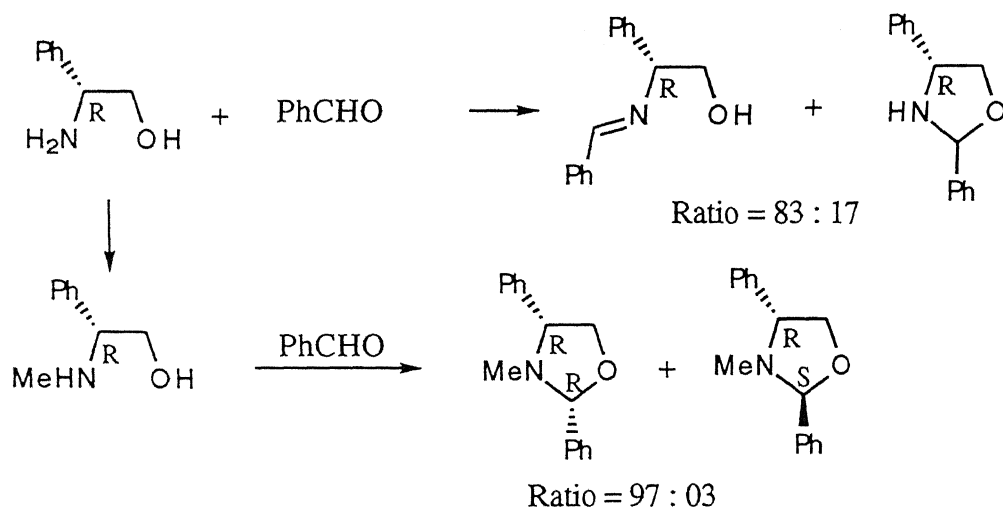
Pridgen and coworker explored the use of 2-aryl-4-phenyl-1,3-oxazolidine **15** as a general substrate for the organometallic addition.⁸ The reaction led to the formation of an adduct **16** which was a source of chiral α -substituted phenethylamine **17** in high level of asymmetric induction (Scheme V).



Scheme V

The chelation effect in the transition state was explored by addition of Lewis acid chelators like ZnCl_2 , TiCl_4 , BF_3OEt_2 , CuI or $\text{CuBr}_2\text{S}(\text{CH}_3)_2$, and they obtained at the best a 77:23 ratio of isomeric products. On the other hand with a 1:1 ratio of cerium chloride to Grignard reagent, only one stereoisomer was obtained. The stronger chelating ability of cerium had enhanced the selectivity of the organometallic addition to the extent that a single diastereomer was produced.

In 1992, Higashiyama *et al.*⁹ obtained good diastereoselectivity in the reaction of MeLi or MeMgBr with chiral aromatic imines and 1,3-oxazolidines derived from (*R*)-phenylglycinol. Unsubstituted phenylglycinol gave a mixture of imine and oxazolidines (83:17 to 93:7) while *N*-substituted phenylglycinol gave diastereomeric mixture of oxazolidines (minor component was less than 10%) on condensation with benzaldehyde (Scheme VI). The imines were found to give (*R,R*)-amines while 1,3-oxazolidines gave (*R,S*)-amines with MeLi and MeMgBr respectively.

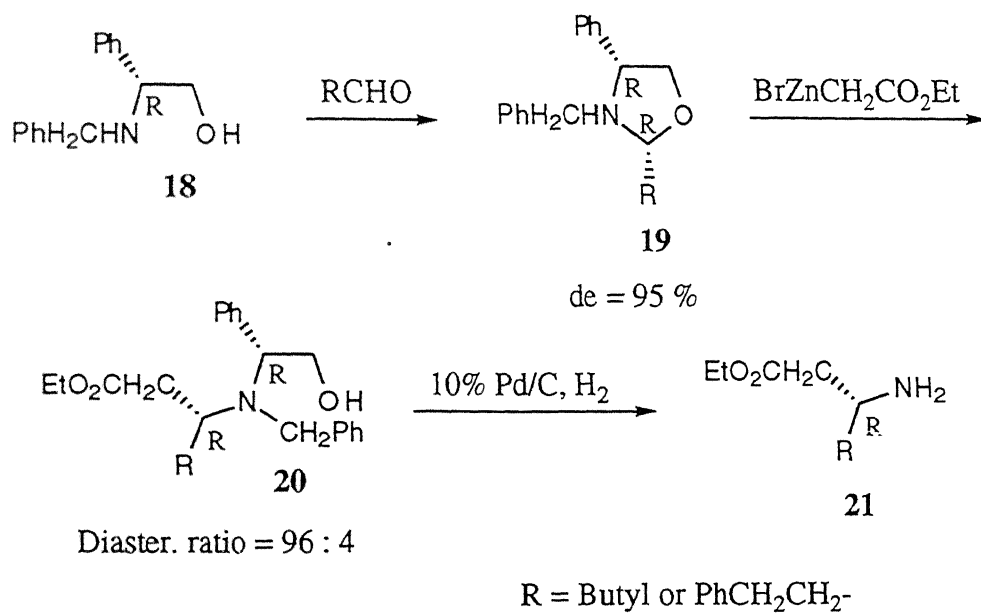


Scheme VI

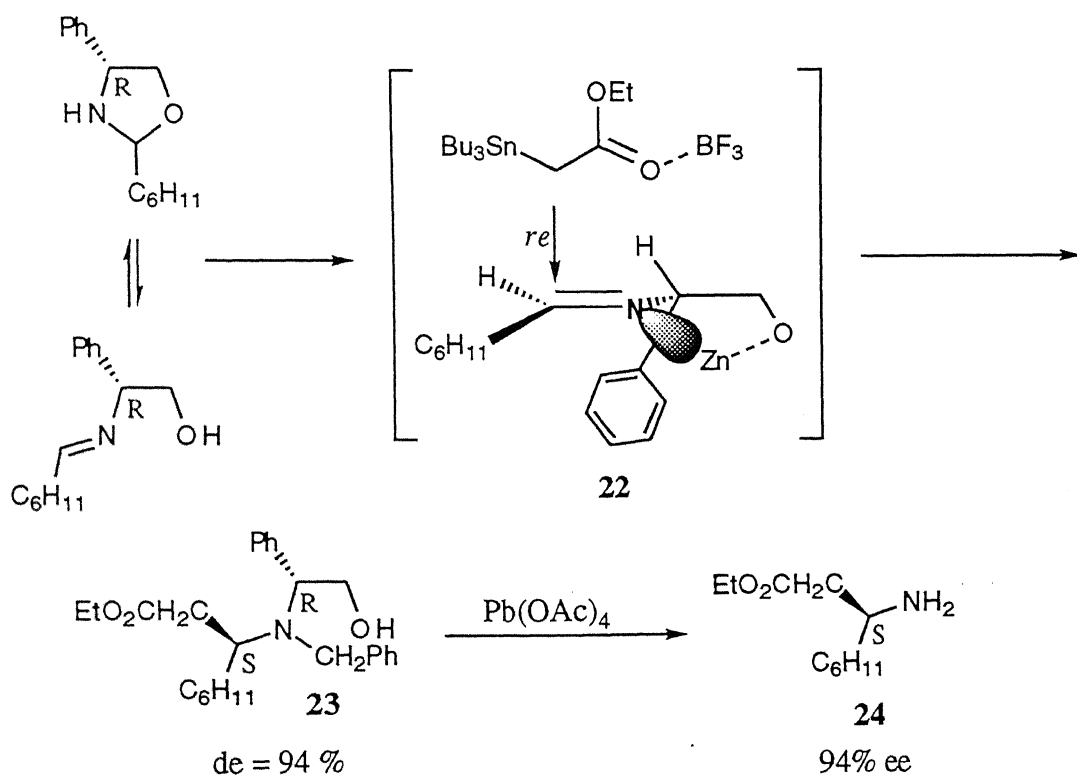
Pedrosa and coworkers¹⁰ showed the stereoselective ring opening of chiral oxazolidines **19** by Reformatsky reagent, $\text{BrZnCH}_2\text{CO}_2\text{Et}$, leading to the formation of β -aminoesters **21**. A maximum ee of 92% was obtained with $\text{R}=\text{butyl}$ or PhCH_2CH_2 - (Scheme VII).

L.N.Pridgen and coworkers¹¹ prepared chiral 2-alkyl-1,3-oxazolidine as a substrate for allyl organocerium stereoselective addition. They were able to get chiral β -aminoacid after several steps. But they also showed that use of highly stable ethyl tributylstannylacetate under Lewis acid condition could lead to the β -aminoester **24** quite efficiently. The most effective Lewis acid

catalyst found to be combination of both ZnCl_2 and BF_3OEt_2 (Scheme VIII). With R as cyclohexyl, they obtained 94% ee for **24**.



Scheme VII



Scheme VIII

The addition of Grignard reagent to the chiral imines and 1,3-oxazolidines obtained from (*R*)-phenylglycinol and aromatic aldehydes led to the asymmetric synthesis of (*R*)-2-aryl- and (*R,R*)-2,5-bis(aryl)pyrrolidines¹², which were useful as a chiral auxiliary for the stereoselective syntheses.

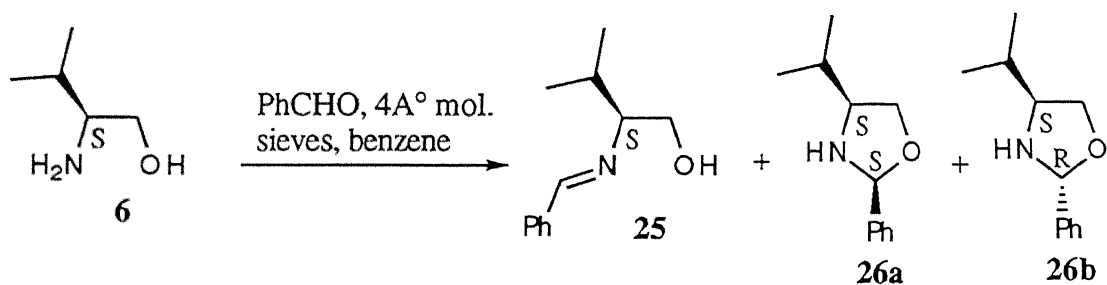
Background

Diastereoselective intermolecular addition of organometallics to the C=N bond of imines and their derivatives, prepared from chiral valinol or phenylglycinol, has been studied a lot and exploited in the synthesis of optically active amines.¹⁻¹⁴ The major drawback with this method is that the condensation of aminoalcohols with aldehydes gives a tautomeric mixture of imines and oxazolidines. In case of oxazolidines, it is even more complicated because these are formed in two diastereomeric forms (*SS* and *SR*). In view of the recent work⁹ that these imines and oxazolidines give different diastereomers on reaction with MeLi or MeMgBr, there is a strong need to prepare these types of compounds in pure form. Once obtained in pure form, they can be utilized for the formation of chiral amines. Another drawback quite evident in all the previous studies was that, due to the presence of mainly hydrophilic groups, the oxazolidines were difficult to purify and characterize. The presence of more hydrophobic groups like phenyl, in the starting aminoalcohols, will enable us to isolate the products and monitor the reactions properly. With this aim, we started the work in this area.

In this chapter, we describe our efforts¹⁵ towards the diastereoselective formation of *SS*-isomer 1,3-oxazolidines derived from (*S*)-2-amino-3-methyl-1,1-diphenylbutane-1-ol or diphenylvalinol¹⁶ and (*S*)-2-amino-2-phenyl-1,1-diphenylethane-1-ol or diphenylphenylglycinol¹⁶, and then the addition of organometallics to them, leading to their opening and ultimate formation of chiral amines.

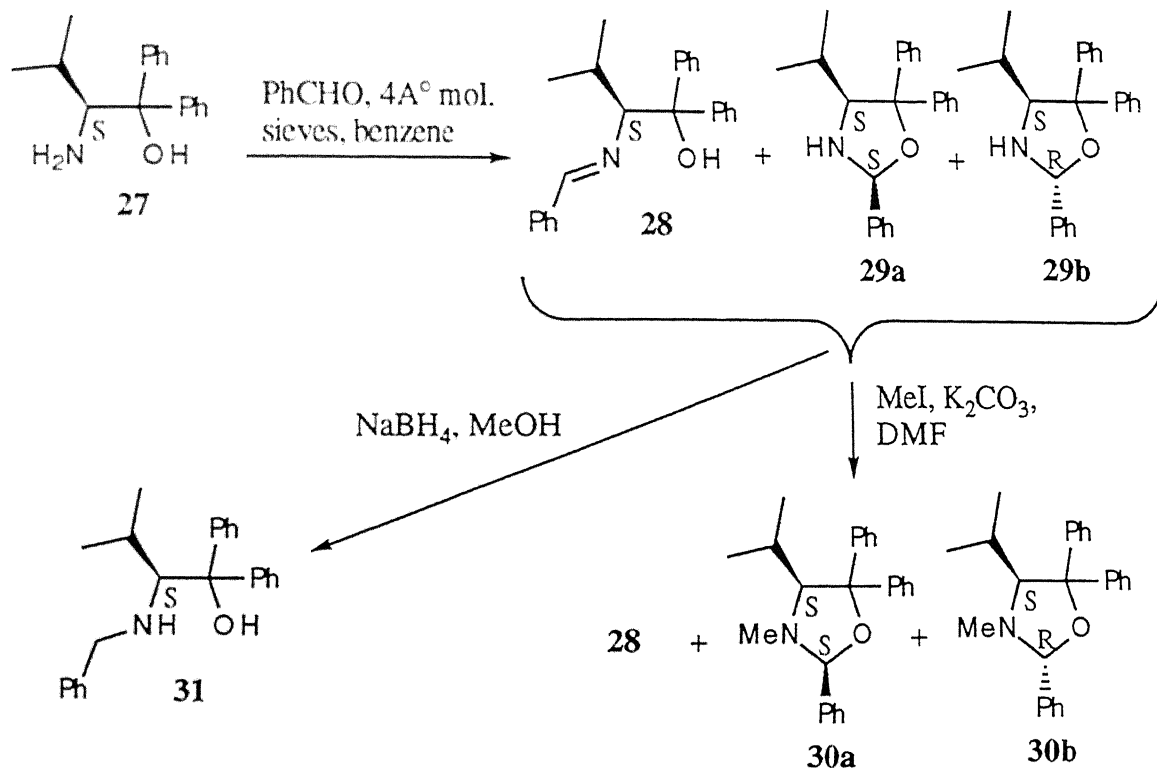
Present work

It has been reported that condensation of (*S*)-valinol **6** and benzaldehyde gives pure imine.² However, when we did the same reaction the ¹H NMR of the crystallized product showed a mixture of imine **25** (sharp singlet at δ 8.8 for Ph-HC=N-) and 1,3-oxazolidine **26** (split singlet at δ 5.27 for N-CHHPh-O) in a 2:1 ratio (Scheme IX). One of the disadvantages with the condensed product from valinol is that it streaks on TLC plate. In view of this difficulty in monitoring the reaction, we decided to explore (*S*)-diphenylvalinol **27**.¹⁶



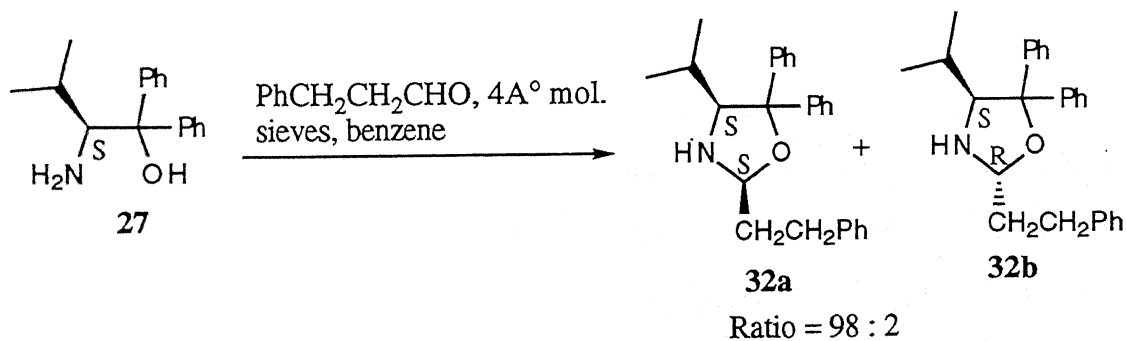
Scheme IX

The reaction of **27** with two types of aldehydes was studied. It was observed that the practical difficulty faced earlier was solved. The phenyl groups made it quite hydrophobic to be easily monitored. The condensation of **27** with benzaldehyde gave a mixture of imine **28** and oxazolidine **29** where the latter was present in major amount. Although the tautomeric ratio of imine and oxazolidine was not consistent and varied to some extent (1:3-5), *SS*-diastereomer (sharp singlet in ¹H NMR at δ 5.46) was always the major one (diastereomeric ratio of *SS*:*SR* = 4:1). The absolute stereochemistry at C-2 of oxazolidine **29** was established based on ¹H NMR spectrum and literature precedence.¹⁷ Although **29** did not show any separation on tlc plate, the N-methylated oxazolidine **30** showed clear cut separation of both the diastereomers on silica gel tlc plates (*SS* is less polar than *SR*). These diastereomers were separated and it was found that the difference lay with the chemical shift of N-CHH-O (δ 4.71 for *SS*-isomer and δ 5.83 for *SR*-isomer). Again when this mixture of **28** and **29** was treated with NaBH₄ in MeOH, **31** was formed as the only product (Scheme X).

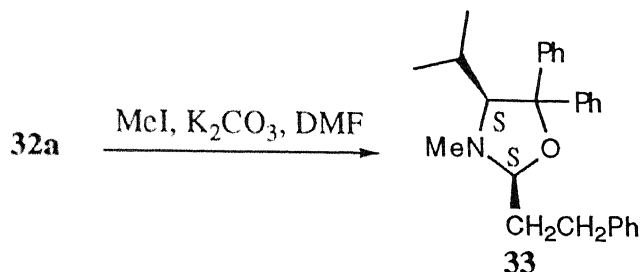


Scheme X

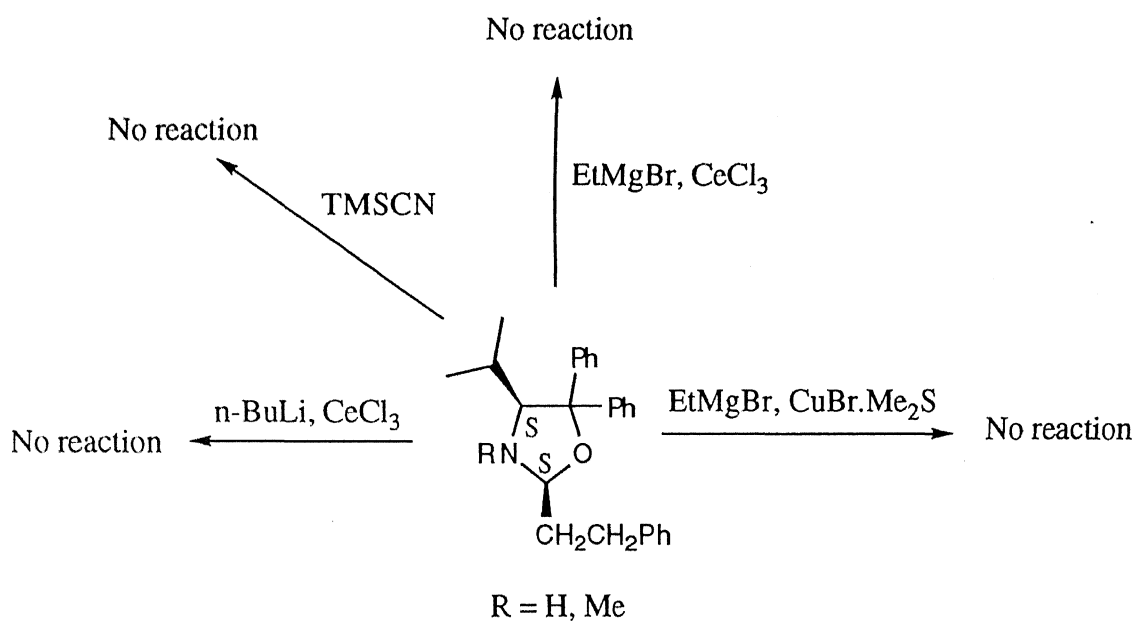
The reaction of (*S*)-diphenylvalinol **27** with hydrocinnamaldehyde gave the oxazolidine **32** diastereoselectively (*SS* : *SR* ratio, 98 : 2 by ^1H NMR). The major *SS*-isomer gave a triplet at δ 4.47 corresponding to N-CH-O proton. The minor one (*SR*-isomer) amounted to less than 2% and showed a triplet at δ 5.02 for the same proton. The added advantage of these oxazolidines is that both diastereomers show separation (*SS* is more polar than *SR*) on silica gel tlc plates. The absolute stereochemistry was assigned based on ^1H NMR data and literature precedence¹⁷ (Scheme XI). The *SS*-isomer of **32** was converted to *N*-methylated product *SS*-**33**, by treatment with MeI and K_2CO_3 in DMF .



Scheme XI



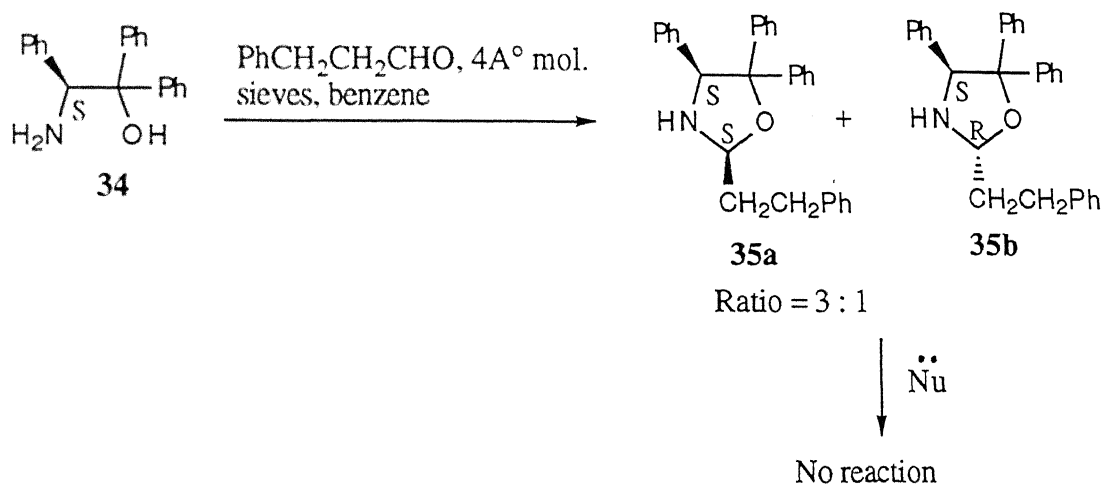
After achieving pure oxazolidines, several nucleophiles were tried for their opening (Scheme XII). But unfortunately, we were not able to be successful under any conditions. Even stronger nucleophiles in combination with lewis acids proved to be ineffective. It may be possible that due to the presence of two bulky phenyl groups at position 5, the reaction was sterically hindered.



Scheme XII

We then turned our attention to (*S*)-diphenylphenylglycinol¹⁶ **34** and carried out its reaction with hydrocinnamaldehyde, we got a mixture of the two oxazolidines (*SS*)-**35a** and (*SR*)-**35b** in the ratio of 3:1 (Scheme XIII). The major *SS*-isomer gave a triplet at δ 4.75 corresponding to N-CH-O proton while the minor one (*SR*-isomer) showed a triplet at δ 5.25 for the same proton in ¹H NMR. In this case the isomerization seemed to occur in the process of the synthesis of **34**. But as our main aim was to open the prepared pure oxazolidines and use them for the synthesis of chiral

amines, we tried the same opening reactions on **35**, the reactions again failed and so we did not proceed further.



Scheme XIII

Conclusion

In summary, we have shown that diphenylvalinol **27**, is a very good auxiliary for preparing 100% diastereomerically pure oxazolidines. Thus we have prepared various pure oxazolidines. We also tried similar reactions with diphenylphenylglycinol **34**. However, we failed to open the oxazolidines with nucleophiles.

Experimental

General considerations

The common materials and methods have been given in the experimental section of Chapter-1. (*S*)-Diphenylvalinol and (*S*)-diphenylphenylglycinol were prepared according to the literature procedure¹⁶. (*S*)-valinol and (*S*)-phenylglycinol was obtained from (*S*)-valine and (*S*)-phenylglycine respectively, following the known method¹⁸. Trimethylchlorosilane and CuBrMe₂S (Copper(I)bromide-dimethyl sulfide) complex were purchased from Fluka. Hydrocinnamaldehyde and cerium(III)chloride heptahydrate (CeCl₃·7H₂O) were Aldrich compounds. Anhydrous potassiumcarbonate and benzaldehyde were bought from S.D.Fine Chem.Ltd. Methyl iodide was obtained from Loba Chemie Pvt. Ltd. Benzene was distilled over sodium and finely ground cerium(III)chloride heptahydrate (CeCl₃·7H₂O) was dried by heating at 140 °C under high vacuum for 2-3 h.

General Procedure for the Condensation of Aminoalcohol with Aldehyde: A solution of the aminoalcohol (1.0 eq.) and aldehyde (1.0 eq.) in benzene was kept at roomtemperature over activated 4Å° molecularsieves for 16 h. Filtration and solvent removal gave the product.

Condensation of (*S*)-valinol 6 with benzaldehyde (Scheme IX): Reaction was performed according to the general procedure. The yield of the crystalline product obtained was quantitative. ¹H NMR (CCl₄, 60 MHz) δ0.60 - 1.16 (m, 6H), 1.56 - 2.30 (m, 1H), 2.10 (s, 1H), 2.63 - 3.10 (m, 1H), 3.63 (m, 2H), 5.27 (split singlet, N-CHPh-O for oxazolidine **26**), 7.00 - 7.80 (m, aromatics), 8.10 (s, Ph-CH=N- for imine **25**).

The inseperable mixture of imine **25** and oxazolidine **26** is in the ratio of 2:1 from ¹H NMR.

Condensation of (*S*)-diphenylvalinol 27 with benzaldehyde (Scheme X): Reaction was performed according to the general procedure. The product was obtained as a mixture of solids **28** and **29** in quantitative yield; mp 140 - 143 °C; R_f 0.59 (10% EtOAc in petroleum ether); [α]_D²⁵ -42.5° (c 1.5, CHCl₃); IR (film) 3479, 1646 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ0.50 (d, J = 6 Hz, (H₃C)₂-CH- of oxazolidine), 0.75 (d, J = 6 Hz, (H₃C)₂-CH- of imine), 0.98 (d, J = 6 Hz, (H₃C)₂-CH- of imine), 1.02 (d, J = 6 Hz, (H₃C)₂-CH- of oxazolidine), 1.80 (m, -CH(CH₃)₂ of oxazolidine), 2.00 (m, -CH(CH₃)₂ of imine), 3.70 (d, J = 5 Hz, C-CH-N of *SR*-isomer), 3.91 (d,

$J = 5$ Hz, C-CH-N of *SS*-isomer), 4.07 (d, $J = 2$ Hz, C-CH-N= of imine), 4.41 (s, NH of imine), 5.46 (s, N-CH-O of *SS*-isomer), 6.12 (s, N-CH-O of *SR*-isomer), 6.90 - 7.90 (aromatics, 15H), 8.2 (s, N=CH-).

An inseparable mixture of imine **28** and oxazolidine **29**, in an inconsistent ratio was found to be formed from ^1H NMR spectrum.

(2*S*, 4*S*)-2-Phenyl-N-methyl-4-isopropyl-5,5'-diphenyl-1,3-oxazolidine 30: A solution of **28** and **29** (450 mg, 1.32 mmol) was treated with MeI (164 mL, 2.62 mmol) in DMF (2 mL) at room temperature in the presence of *anhyd.* K_2CO_3 (362 mg, 2.62 mmol) for 16 h. Most of the DMF was removed in *vacuo*, the crude mixture was dissolved in ether and washed with water. Drying and solvent removal gave the N-methylated oxazolidines **30** (*SS* vs *SR* = 4:1) along with 50% unreacted material which was further recycled. Compound was purified by silica-gel column chromatography gave pure *SS*-isomer **30a** (140 mg) as a solid compound; mp 91 - 92 °C; R_f 0.69 (5% EtOAc in petroleum ether); $[\alpha]_D^{25} -52.3^\circ$ (c 2.0, CHCl_3); ^1H NMR (CCl_4 , 60 MHz) δ 0.67 (d, $J = 6.4$ Hz, 3H), 0.90 (d, $J = 6.4$ Hz, 3H), 1.72 (m, 1H), 2.28 (s, 3H), 3.55 (d, $J = 3.5$ Hz, 1H), 4.71 (s, 1H, N-CH-O), 7.0 - 7.8 (aromatics, 15H); Anal. Calcd. for $\text{C}_{25}\text{H}_{27}\text{NO}$: C, 84.03; H, 7.56; N, 3.92. Found: C, 83.86; H, 7.65; N, 3.87.

N-benzyl-(*S*)-diphenylvalinol 31: To a solution of **28** and **29** (210 mg, 0.612 mmol) in MeOH (2 mL), NaBH_4 (139 mg, 3.67 mmol) was added in portions at 0 °C. After 3 h of stirring, MeOH was removed. The reaction mixture was taken in ether and washed with water. Organic extracts were dried and solvent was removed. Column chromatography gave **31** as pure product. Yield 64%; R_f 0.50 (5% EtOAc in petroleum ether); IR (neat) 3370, 3040, 2960, 1490, 1445 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 0.71 (d, $J = 6$ Hz, 3H), 0.97 (d, $J = 6$ Hz, 3H), 2.10 (m, 1H), 3.30 (d, $J = 8$ Hz, 1H), 3.45 (d, $J = 8$ Hz, 1H), 3.64 (d, 1H), 7.11 - 7.73 (aromatics, 15H).

Condensation of (*S*)-diphenylvalinol 27 with hydrocinnamaldehyde (Scheme XI): Reaction was performed according to the general procedure. The column chromatography provided **32a** as a viscous liquid. Yield 95%; R_f 0.45 (1:9 EtOAc in petroleum ether); $[\alpha]_D^{25} -46.91^\circ$ (c 5.0, CHCl_3); IR (film) 3083, 3059, 3024, 1450, 1010 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 0.46 (d, $J = 6.6$ Hz, 3H), 1.00 (d, $J = 6.7$ Hz, 3H), 1.77 (m, 1H), 1.92 (bs, 1H, NH), 2.25 (m, 2H), 2.94 (m, 2H), 3.71 (d, $J = 4.8$ Hz, 1H), 4.47 (t, $J = 5.8$ Hz, 1H), 7.10 - 7.60

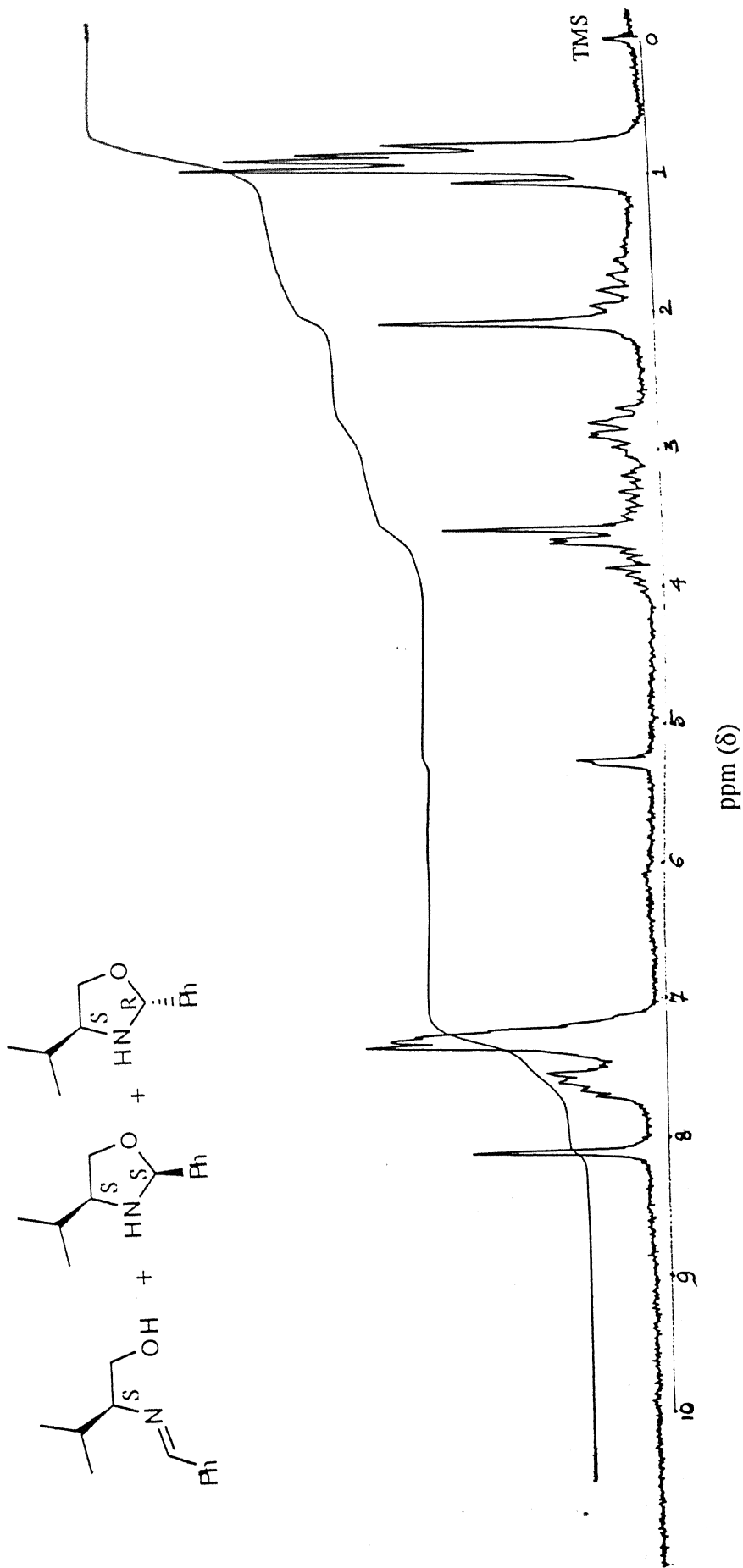
(aromatics, 15H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 17.7 (CH_3), 22.7 (CH_3), 28.6 (CH), 32.0 (CH_2), 35.6 (CH_2), 73.5 (CH), 87.3 (quat. C), 89.2 (CH), 125.8 - 128.6 (CH of aromatic rings), 141.5, 143.6 and 146.0 (quat. C of the three aromatic rings); Anal. Calcd. for $\text{C}_{26}\text{H}_{29}\text{NO}$: C, 84.10; H, 7.82; N, 3.77. Found: C, 84.05; H, 7.90; N, 3.80.

(2S, 4S)-2-Phenethyl-N-methyl-4-isopropyl-5,5'-diphenyl-1,3-oxazolidine 33: A solution of **32a** (200 mg, 0.54 mmol) and MeI (154 mg, 1.08 mmol) in DMF (1 mL) was stirred at room temperature, in the presence of *anhyd.* K_2CO_3 (150 mg, 1.08 mmol) for 16 h. Most of the DMF was removed in *vacuo*, the crude mixture was dissolved in ether and washed with water. Drying, solvent removal and purification of the residue over silica gel gave 180 mg of **33** as a solid. Yield 87%; mp 99 - 100 °C; R_f 0.79 (10% EtOAc in petroleum ether); $[\alpha]^{25}_{\text{D}} -62.44^\circ$ (c 2.2, CHCl_3); IR (film) 3082, 3066, 3028, 1450, 700 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 0.63 (d, $J = 6.54$ Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H), 1.70 (m, 1H), 2.08 (m, 2H), 2.26 (s, 3H), 2.90 (m, 2H), 3.51 (d, $J = 3.22$ Hz, 1H), 3.91 (dd, $J = 6.3$ Hz, 3.5 Hz, 1H), 7.05 - 7.60 (aromatics, 15H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 16.9 (CH_3), 22.1 (CH_3), 30.1 (CH), 31.6 (CH_2), 35.6 (CH_2), 41.5 (CH_3), 75.7 (CH), 88.4 (quat. C), 94.7 (CH), 125.6 - 128.4 (CH of aromatic rings), 142.4, 143.0 and 148.1 (quat. C of three aromatic rings); Anal. Calcd. for $\text{C}_{27}\text{H}_{31}\text{NO}$: C, 84.16; H, 8.05; N, 3.64. Found: C, 84.12; H, 8.10; N, 3.70.

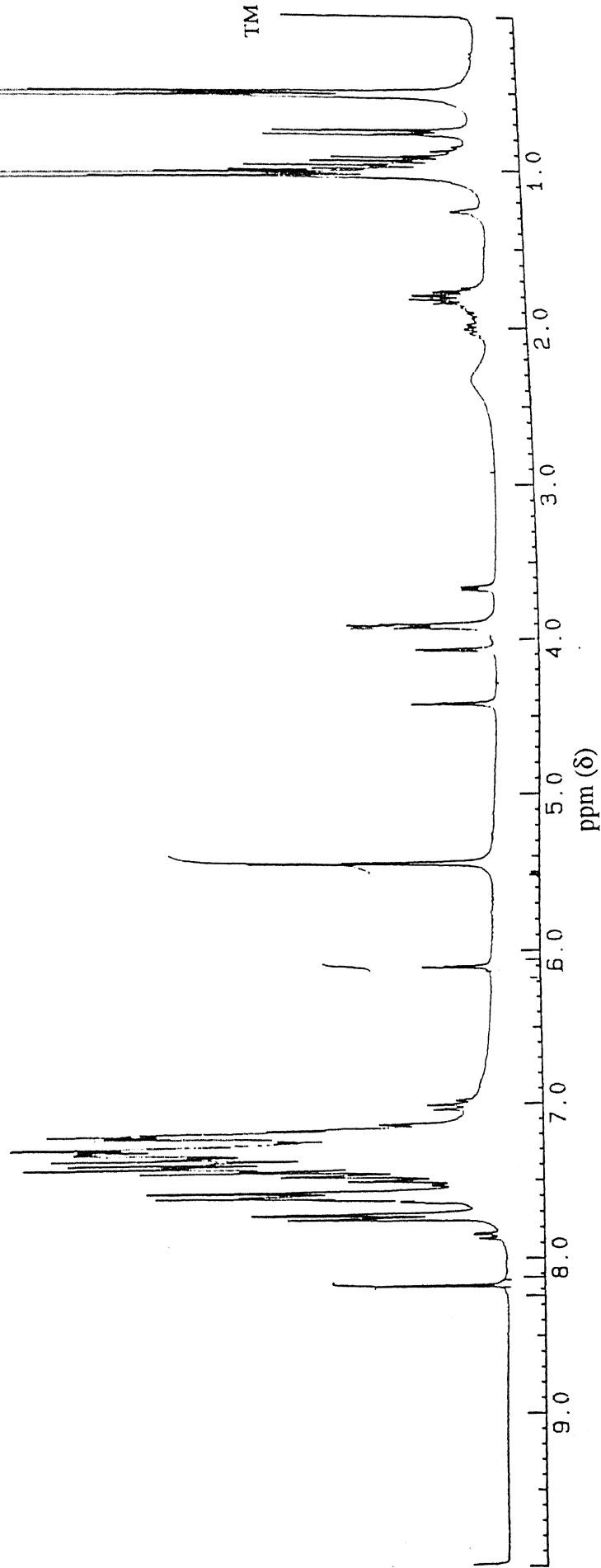
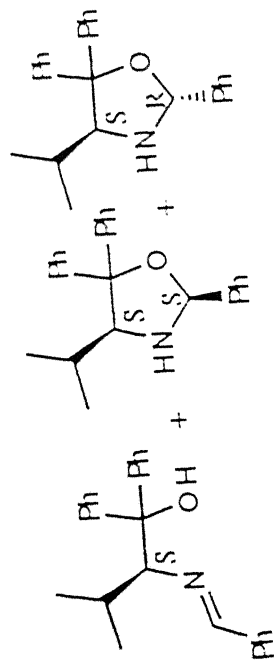
Condensation of (S)-diphenylphenylglycinol **34** with hydrocinnamaldehyde

(Scheme XIII): Reaction was performed according to the general procedure. The column chromatography provided **35** as a viscous liquid. Yield 95%; R_f 0.64 (20% EtOAc in petroleum ether); $[\alpha]^{25}_{\text{D}} -26.34^\circ$ (c 3.0, CHCl_3); IR (film) 3280, 3060, 3020, 1440, 1020 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 2.25 (m, 2H), 2.95 (m, 2H), 4.75 (t, $J = 5.5$ Hz, for *SS*-diastereomer **35a**), 5.03 (s, 1H), 5.25 (t, $J = 6$ Hz, for *SR*-diastereomer **35b**), 6.83 - 7.65 (aromatics, 20H).

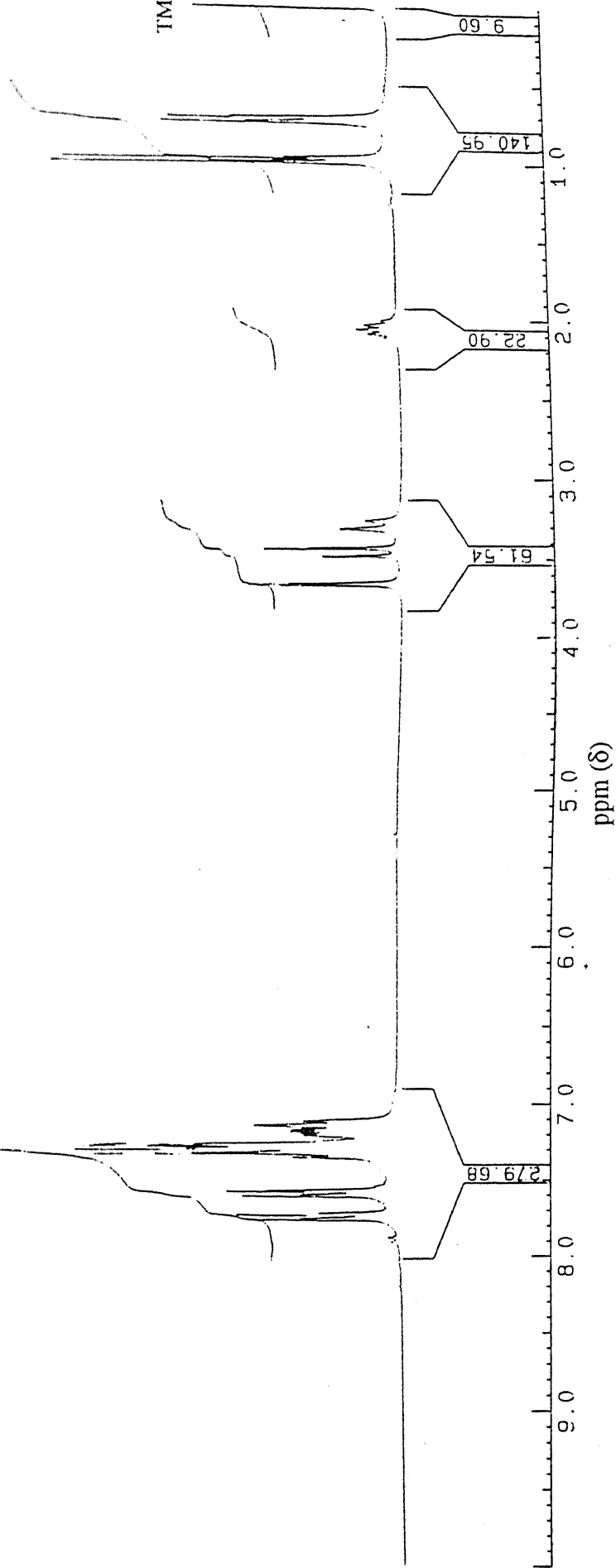
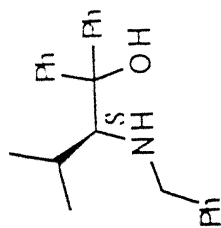
From ^1H NMR the ratio of **35a** and **35b** was found to be 3:1.



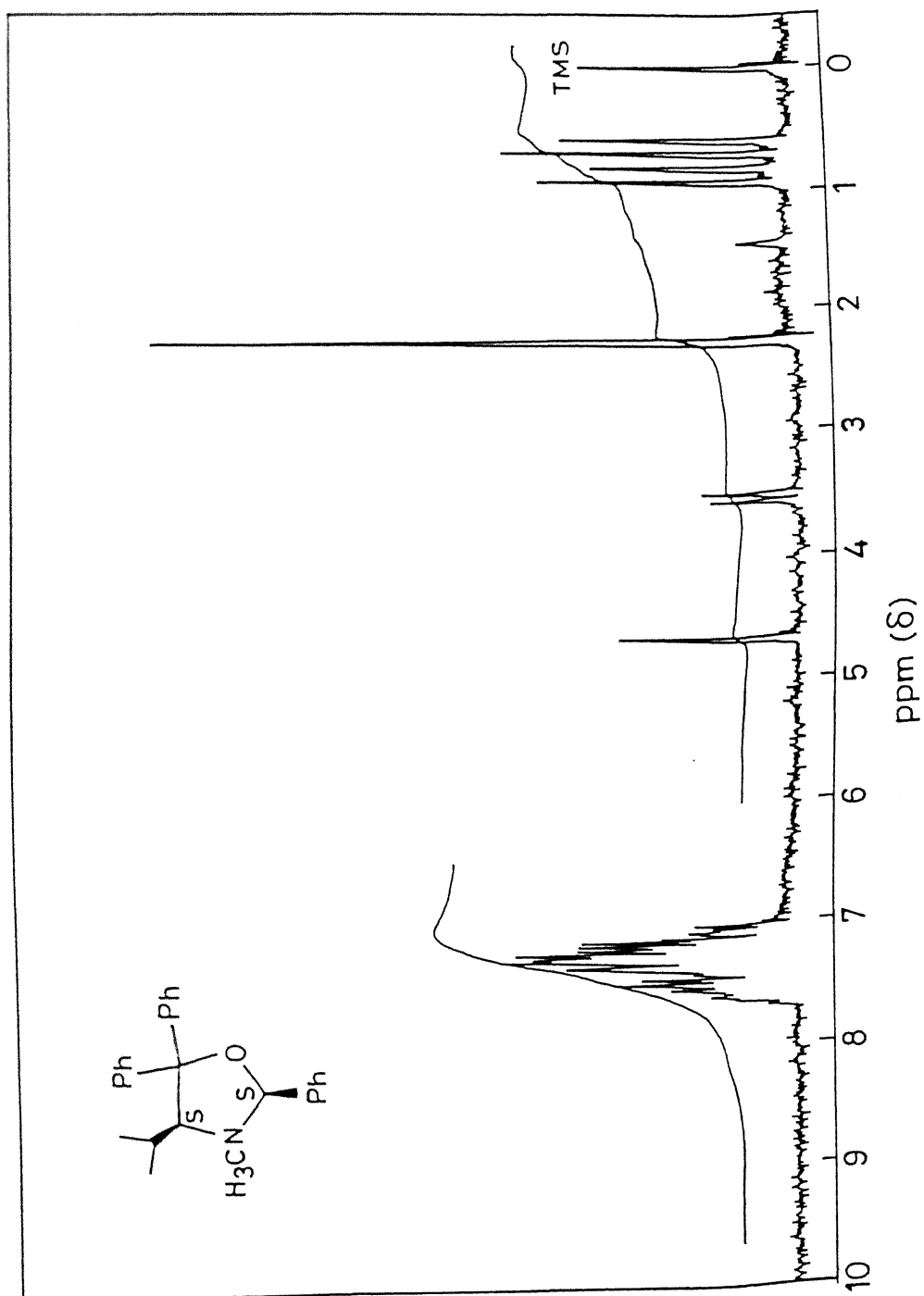
60 MHz ${}^1\text{H}$ NMR spectrum of the mixture of **25** and **26** in CCl_4 .

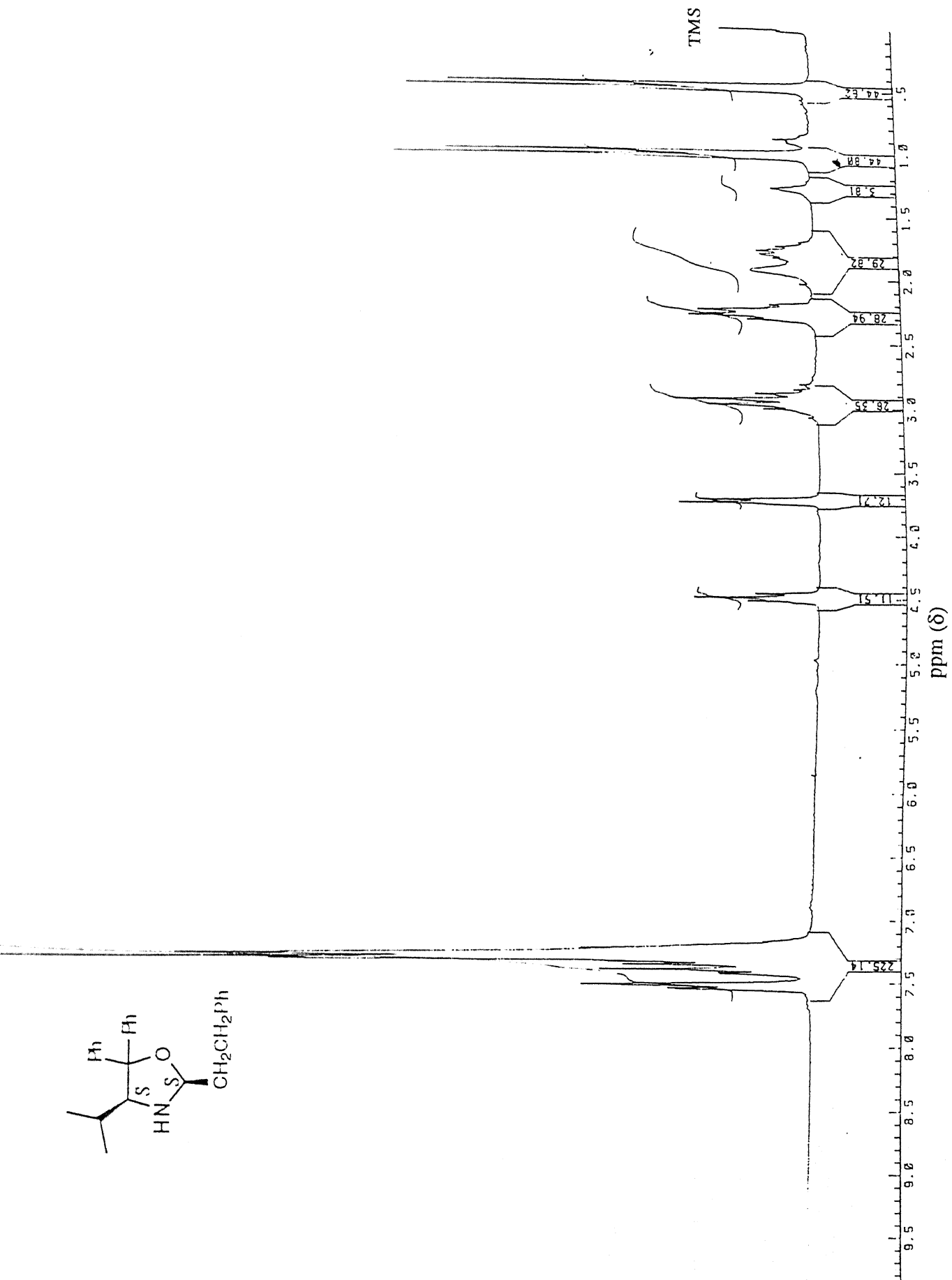


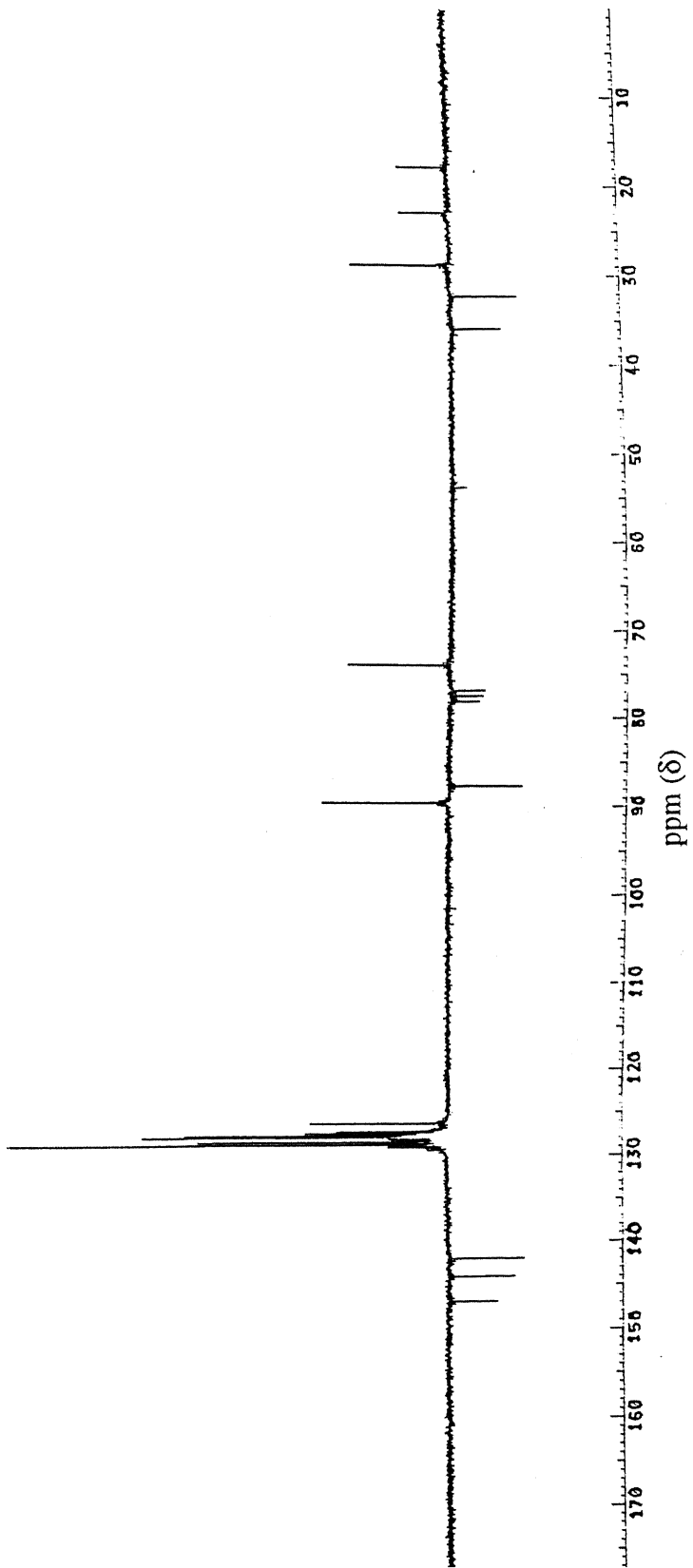
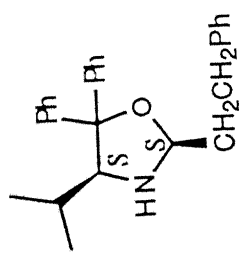
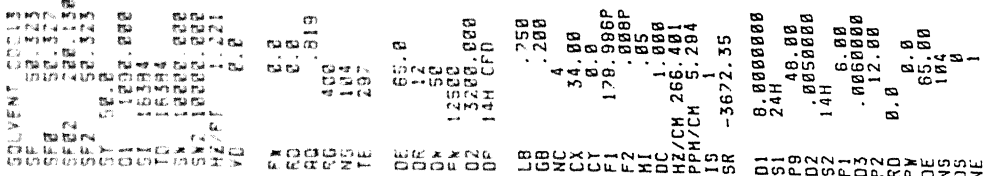
200 MHz ^1H NMR spectrum of the mixture of **28** and **29** in CDCl_3 .



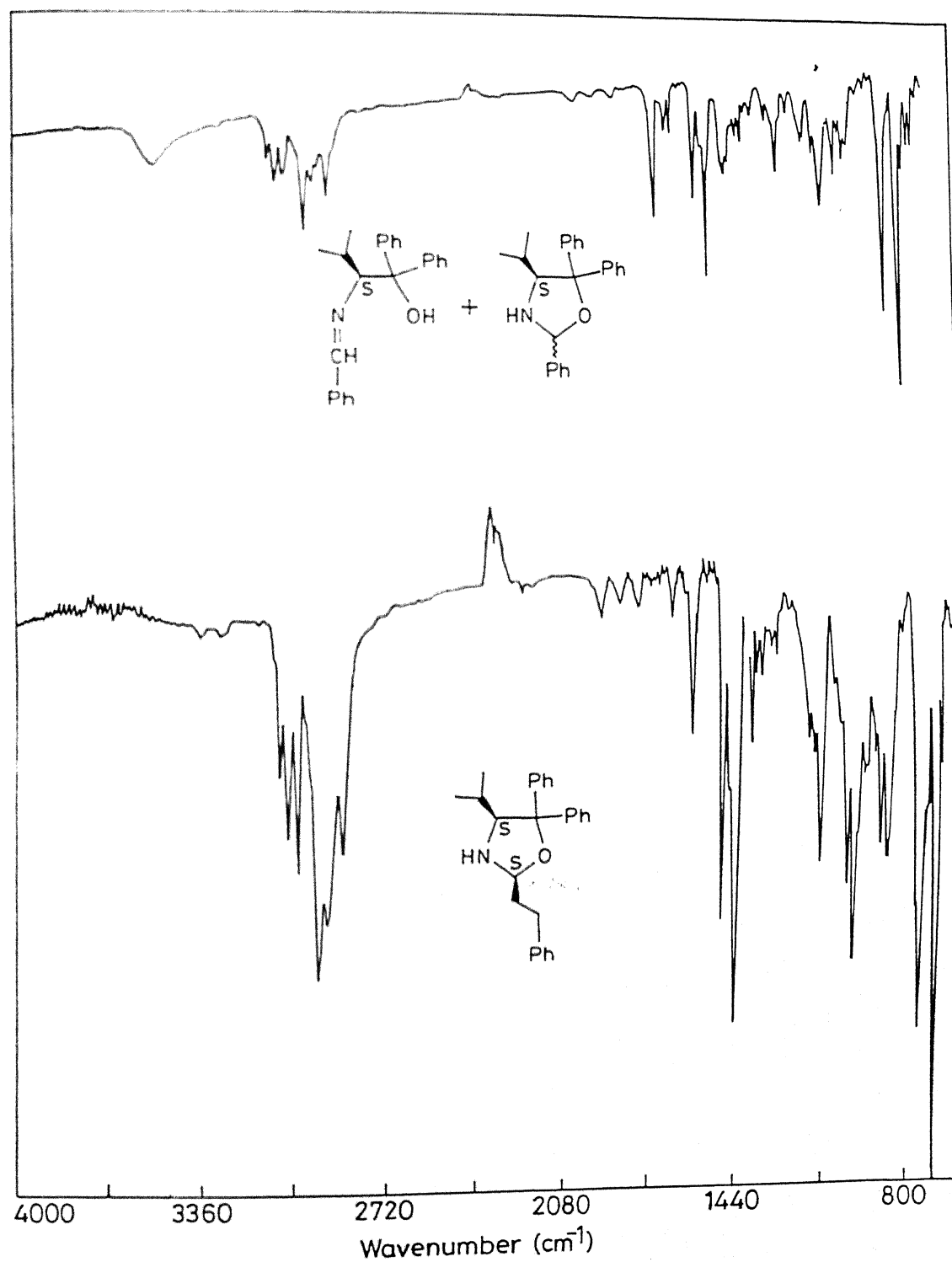
200 MHz ^1H NMR spectrum of **31** in CDCl_3 .

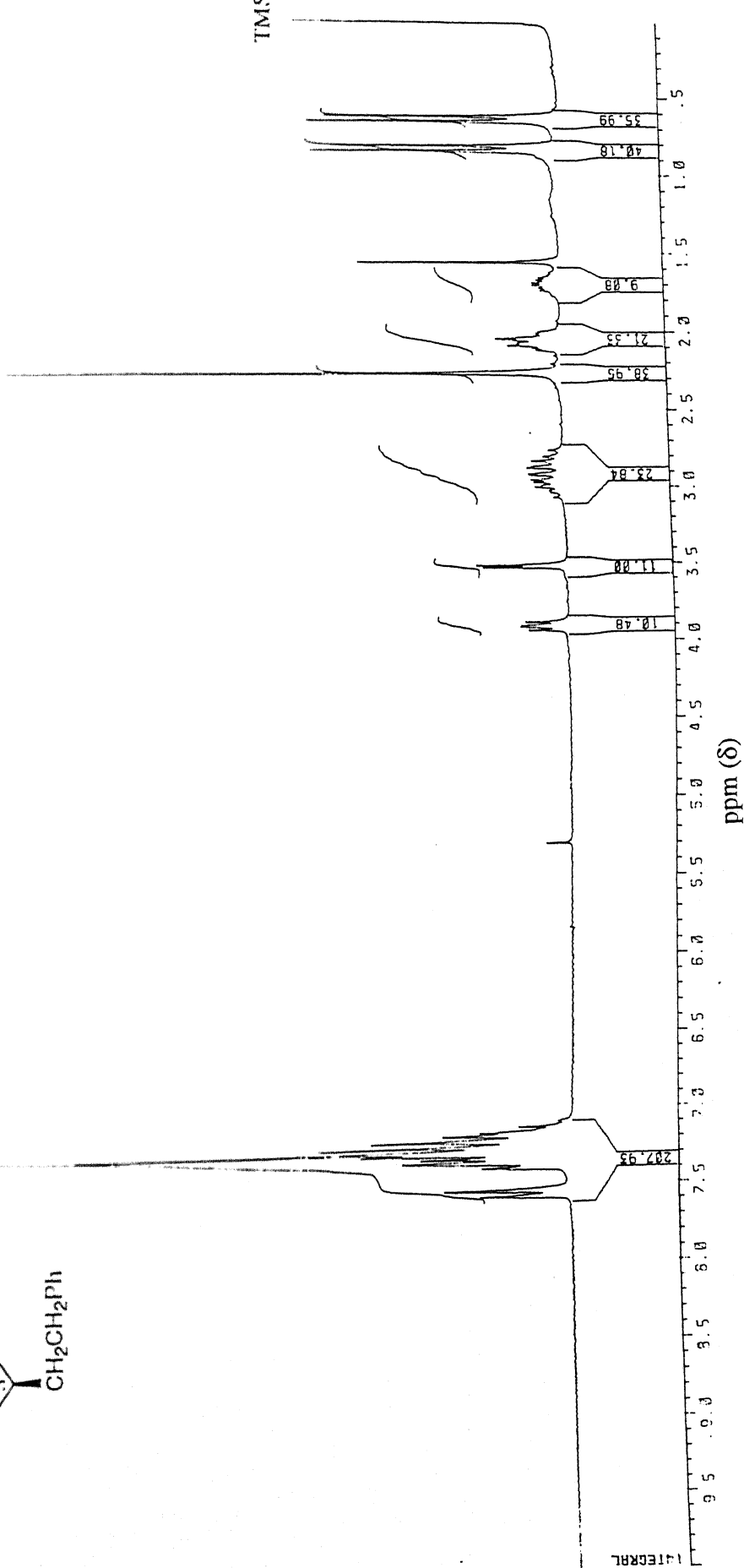
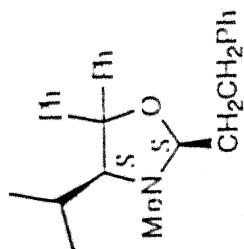




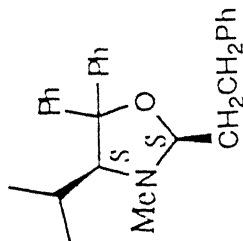


50 MHz ^{13}C NMR spectrum of **32a** in CDCl_3 .

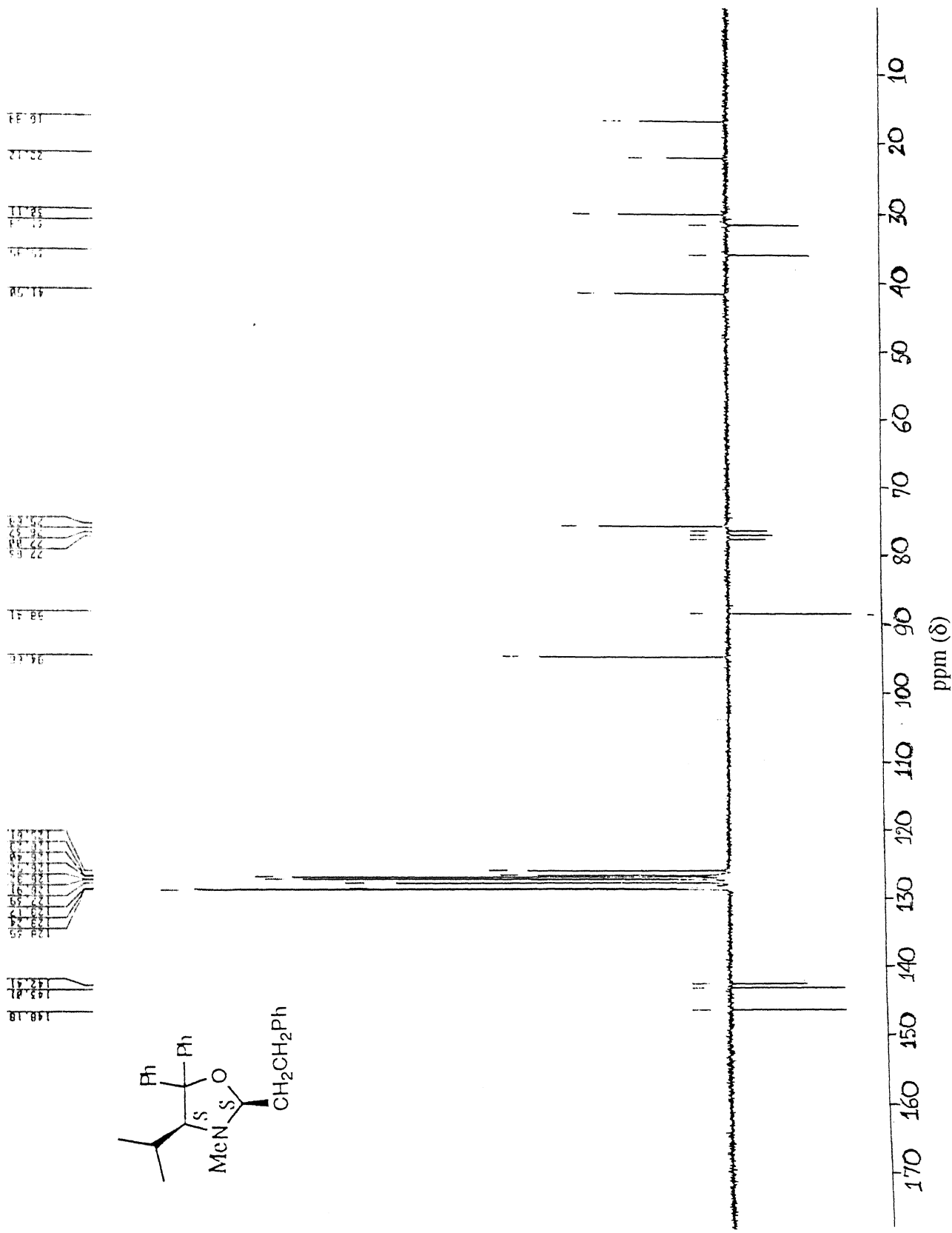




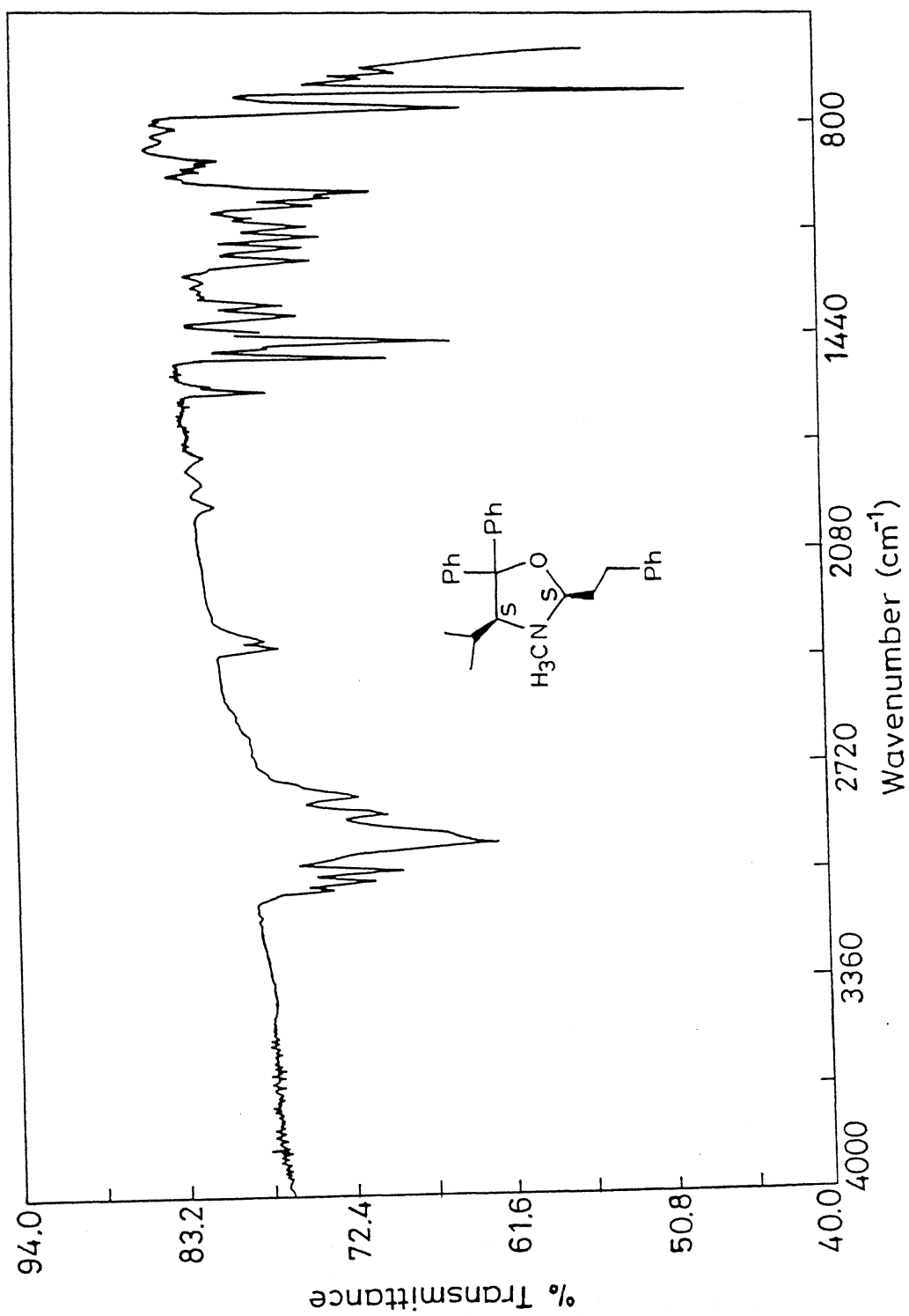
200 MHz ^1H NMR spectrum of **33** in CDCl_3 .



SR. 381
 AU PROG: JH00XH.AUR
 DATE 23-6-92
 TIME 15:14
 SOLVENT CDCl₃
 SF 50.323
 SF0 50.322
 SF02 200.130
 SF2 50.323
 SY 50.11
 O1 100.000
 SI 16384
 IO 16384
 SW 9615.385
 SW2 9615.385
 HZ/PT 1.174
 VO 0.0
 PV 0.0
 RD 0.0
 AQ 0.852
 RG 400
 NS 98
 TE 297
 DE 67.5
 OR 12
 OV 52
 FV 12100
 O2 3200.000
 OP 14H CPD
 LB 0.600
 GB 0.0
 NC 3
 CX 34.30
 CY 0.0
 FI 160.300P
 F2 0.007P
 VI 0.32
 CC 1.000
 HZ/CM 266.407
 PH/CM 5.294
 IS 5
 SR -3669.91
 J1 8.1000000
 S1 24H
 P9 48.30
 D2 3050000
 Z2 14H
 P1 6.30
 D3 0.000000
 P2 0.0
 RD 0.0
 PW 67.50
 DE 98
 NS 0
 DS 1
 NE 1



50 MHz ¹³C NMR spectrum of **33** in CDCl₃.



IR spectrum (neat) of 33.

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<i>Thesis supervisor</i>	Dr. Vinod K. Singh

Publications:

- Recent Aspects of Enantioselective Epoxidation of Olefins
 (A. D. Gupta, D. Bhuniya, and V. K. Singh *J. Indian. Inst. Sci.* **1994** , 74, 71).
- Diastereoselective Formation of (2*S*, 4*S*)-1,3-Oxazolidines from (*S*)-Diphenylvalinol
 (A. DattaGupta, B. Singh and V. K. Singh *Indian. J. Chem.* **1994**, 33B, 981).

4. Synthesis of Versatile Intermedites for Cyclopentanoid Natural Products via Enantioselective Deprotonation of substituted Cyclopentene Oxide (D. Bhuniya, A. DattaGupta, and V. K. Singh *Tetrahedron Lett.* **1995**, 36, 2847).
5. A Mild Method for the Cleavage of tert-Butyldimethylsilyl and Tetrahydropyranyl Ethers by Ceric Ammonium Nitrate (A. DattaGupta, R. Singh, and V. K. Singh *Synlett* **1996**, 69).
6. Catalytic Enantioselective Allylic Oxidation of Olefins with Copper Complexes of Chiral Nonracemic Bis(oxazoliny)pyridine type ligands (A. DattaGupta and V. K. Singh *Tetrahedron Lett.* **1996**, 37, 2633).
7. Design, Synthesis, and Application of Chiral Nonracemic Lithium Amide Bases in Enantioselective Deprotonation of Epoxides (Debnath Bhuniya, Arpita DattaGupta, and Vinod K. Singh *J. Org. Chem.* **1996**, 0000.)
8. Catalytic Enantioselective Cyclopropanation of Olefins using Carbenoid Chemistry (Vinod K. Singh, Arpita DattaGupta, and G. Sekar *Synthesis* **1996**, accepted).